REMARKS

Upon entry of this amendment, claims 22, 32, 33, 36-41, 51, 55-61, 64-68 and 71-74 will be pending and under consideration. Claims 22 and 65 have been amended to more clearly claim the invention disclosed in the present application. Claims 69 and 70 have been canceled herein without prejudice. No new matter is added by these amendments to the claims.

1. Rejection under 35 U.S.C. § 112, First Paragraph

Claims 23, 32-33, 36-41, 51, 55-61 and 64-74 are rejected under 35 U.S.C. § 112, first paragraph, allegedly, because the specification, while being enabling for the treatment of bacterial infections using liposome encapsulated povidone iodine, does not reasonably provide enablement for the use of the various compounds recited in claim 70. In response, Applicants note that claims 69 and 70 have been canceled, thus obviating that portion of the rejection.

The Examiner also alleges that claims 23, 32-33, 36-41, 51, 55-61 and 64-74 lack enablement in that it would be undue experimentation to treat non-bacterial disease with povidone iodine view of the alleged "unpredictability in the art of the treatment of viral and fungal diseases using povidone iodine". Applicants respectfully disagree.

Under 35 U.S.C. § 112, a patent applicant's specification which contains a teaching of how to make and use the invention must be taken as enabling unless the Patent and Trademark Office provides sufficient reason to doubt the accuracy of the disclosure. *In re Marzocchi*, 439 F.2d 220, 223 24, 169 U.S.P.Q. 367, 369 70 (C.C.P.A. 1971). The claimed invention disclosed in the specification cannot be questioned on the unsupported skepticism of the Examiner. *Ex parte Linn*, 123 U.S.P.Q. 262 (PTO Bd. Pt. App. Int. 1959); *Ex parte Rosenwald*, 123 U.S.P.Q. 261 (PTO Bd. Pt. App. Int. 1959). An invention is enabled even though the disclosure may require some routine experimentation to practice the invention. *Hybritech Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1384, 231 U.S.P.Q. 81, 94 (Fed. Cir. 1986). The fact that the required experimentation may be complex does not necessarily make it undue, if the art typically engages in such experimentation. *M.I.T. v A.B. Fortia*, 774 F.2d 1104, 227 U.S.P.Q. 428 (Fed. Cir. 1985). A considerable amount of experimentation is permitted if it is merely routine or the specification provides a reasonable amount of guidance and direction to the experimentation. *In re Wands*, 858 F.2d 731, 8 U.S.P.Q.2d 1400 (Fed. Cir. 1988); *In re Jackson*, 217 U.S.P.Q. 804, 807 (PTO Bd. Pt. App. Int. 1982). Finally, the Examiner has the burden of showing that the disclosure entails undue experimentation. *In re Angstadt*, 537 F.2d 498, 190 U.S.P.Q. 214 (C.C.P.A. 1976).

Applicants respectfully submit that the Examiner has not shown that one skilled in the art would have had to engage in undue experimentation in order to practice the claimed methods. The rejection is unsound as the Examiner provides only conclusory statements that the claimed invention is not properly supported. Specifically, the Examiner offers no evidence or sound scientific argument to support the contention that one skilled in the art would require examples of methods for treating a non-bacterial infection with povidone iodine in order to practice the claimed invention without undue experimentation. The Examiner does not explain why the disclosure in the specification teaching treatment of an infection in the lower respiratory tract by administering a liposomal formulation of povidone iodine do not adequately support the claimed methods. Section 112 does not require testing of the methods encompassed by the claims. An invention is enabled when the amount of experimentation required to practice the invention is routine and the specification provides a reasonable amount of guidance and direction to the experimentation.

Here, the specification provides considerable guidance and direction to practice the claimed invention. The Examiner's attention is invited to the specification at pages 18-19 which shows the of ability of povidone iodine to kill *Staphylococcus aureus*, and which teaches that the virucidal and chlamydicidal (yeast) activity of povidone iodine is well known in the art and in particular, povidone iodine is highly effective against Herpes Simplex virus type 1 and Adenovirus type 8. It is well known in the art that povidone iodine is a highly effective, broad spectrum topical microbiocide. Applicants respectfully remind the Examiner that a patent preferably omits what is well known in the art. *See, Hybritech, Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 231 U.S.P.Q. 81 (Fed. Cir. 1986).

Moreover, additional data exists that clearly demonstrates that povidone iodine is a effective against bacteria, viruses and fungi. The Examiner's attention is invited to International Patent Publication WO 85/00112 which is cited by the Examiner in the currently outstanding office action, and in particular to page 5 of the publication. As taught therein, povidone iodine has microbiocidal activity, not merely bacteriostatic but broad spectrum microbiocidal activity to kill both gram-positive and gram-negative bacteria (including antibiotic-resistant strains), tubercle bacillus, fungi, viruses, protozoa and yeasts, and this activity is maintained in the presence of blood, pus, serum and mucosal secretions.

Applicants respectfully submit that the foregoing demonstrates, consistent with the teaching in the present specification, that povidone iodine is able to kill a wide variety of microorganisms, including bacteria, viruses and fungi.

An invention meets the standard for successful practice set by Section 112 unless the invention is "totally incapable of achieving a useful result." *Brooktree v. Advances Micro Devices*, 977 F.2d 1555, 24 U.S.P.Q.2d 1401, 1412 (Fed. Cir. 1992). The Examiner's attention is directed to the opinion of the Court of Appeals for the Federal Circuit (Federal Circuit) in *In re Brana*, 51 F.3d 1560, 34 U.S.P.Q.2d 1437 (Fed. Cir. 1995). In *Brana*, the Board had affirmed a final rejection under Section 112, 1st paragraph, of claims covering certain compounds asserted to be useful as anti-tumor substances because it was alleged that the specification was non-enabling since it did not sufficiently establish that the claimed compounds had a practical utility, *i.e.*, as anti-tumor agents. 34 U.S.P.Q.2d at 1439.

The Federal Circuit emphatically reversed the Board's decision. First, it explained the legal standard for compliance with the relevant Section 112 requirement, explaining that "unless there is reason to doubt the objective truth of the statements contained [in the specification] which must be relied on for enabling support", a specification's disclosure "must be taken as in compliance with the enabling requirement." *Id.* at 1441 (emphasis in the original). Further, the *Brana* Court made clear that the Patent and Trademark Office has the initial burden of challenging a presumptively correct assertion of utility; evidence must be presented that those of skill in the art would doubt the disclosure. Only then must the applicant provide rebuttal evidence.

Second, the Federal Circuit explained that even if one of skill in the art would have questioned the asserted utility, all applicants need do to overcome the rejection is to proffer sufficient evidence to convince one skilled in the art of the asserted utility. *Id.* at 1441.

In the *Brana* situation, the Court found that the Patent and Trademark Office had not met its initial burden. Further, the Court held that even if the Patent and Trademark Office had met its burden, the evidence proffered was clearly sufficient to meet the statutory requirement. As explained by the Court:

> We hold as we do because it is our firm conviction that one who has taught the public that a compound exhibits some desirable pharmaceutical property in a standard experimental animal has made a significant and useful contribution to the art, even though it may eventually appear that the compound is without value in the treatment of humans. *Id.* at 1442 [quoting *In re Krimmel*, 292 F.2d 948, 953 (C.C.P.A. 1961)].

The Federal Circuit further reminded the Commissioner that testing for the full safety and effectiveness of a product is more properly left to the Food and Drug Administration and the requirements under the law for obtaining a patent should not be confused with the requirements

for obtaining government approval to market a particular drug for consumption. *Id.* at 1442; *see*, *Scott v. Finney*, 34 F.3d 1058, 32 U.S.P.Q.2d 1115 (Fed. Cir. 1994).

Undue experimentation is experimentation that would require a level of ingenuity beyond what is expected from one of ordinary skill in the field. *Fields v. Conover*, 170 U.S.P.Q. 276, 279 (C.C.P.A. 1971). The factors that can be considered in determining whether an amount of experimentation is undue have been listed in *In re Wands*, 858 F.2d 731, 8 U.S.P.Q.2d 1400, 1404 (Fed. Cir. 1988). Among these factors are: the amount of effort involved, the guidance provided by the specification, the presence of working examples, the amount of pertinent literature and the level of skill in the art. The test for undue experimentation is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine. *Id.*

While the predictability of the art can be considered in determining whether an amount of experimentation is undue, mere unpredictability of the result of the experiment is not a consideration. Indeed, the Court of Custom and Patent Appeals has specifically cautioned that the unpredictability of the result of an experiment is not a basis to conclude that the amount of experimentation is undue in *In re Angstadt*, 537 F.2d 498, 190 U.S.P.Q. 214 (C.C.P.A. 1976):

> [If to fulfill the requirements of 112, first paragraph, an applicant's] disclosure must provide guidance which will enable one skilled in the art to determine, with reasonable certainty before performing the reaction whether the claimed product will be obtained, . . . then all "experimentation" is "undue" since the term "experimentation" implies that the success of the particular activity is uncertain. Such a proposition is contrary to the basic policy of the Patent Act.
>
> *Id.* at 219 (emphasis in the original).

In view of the above amendments and remarks, it is submitted that the specification provides sufficient teaching to allow one skilled in the art to successfully practice the claimed methods, *i.e.*, treating an infection in the lower respiratory tract by administering liposomes containing povidone iodine, without undue experimentation. This rejection under Section 112, therefore, should be withdrawn.

2. Rejection under 35 U.S.C. § 112, Second Paragraph

Claims 65 and 66 are rejected under 35 U.S.C. § 112, second paragraph, as, allegedly, being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. In particular, the Examiner states that claims 65 and 66,

which recite trachea and bronchi, are inconsistent with claim 22 which recites lower respiratory tract.

Applicants respectfully disagree. The "distinctly claim" requirement of 35 U.S.C. § 112, second paragraph, means that the claims must have a clear and definite meaning when construed in light of the complete patent document. *Standard Oil Co. v. American Cyanamide Co.*, 774 F.2d 448, 227 U.S.P.Q. 293 (Fed. Cir. 1985). The test of definiteness is whether one skilled in the art would understand the bounds of the claim when read in light of the specification. *Orthokinetics, Inc. v. Safety Travel Chairs, Inc.*, 806 F.2d 1565, 1 U.S.P.Q.2d 1081 (Fed. Cir. 1986). A claim need not describe the invention, such description being provided by the specification's disclosure section. *Id.*

Applicants invite the Examiner's attention to page 1, first paragraph, and to page 3, second full paragraph, of the specification which clearly and unambiguously teaches that the lower respiratory tract includes the trachea, bronchi and alveoli. Accordingly, in view of the definition in the specification, lower respiratory tract would be understood by those of skill in the art to include the trachea, bronchi and alveoli. Thus, Applicants respectfully request withdrawal of this Section 112 rejection.

3. Double Patenting

With regard to the provisional obviousness-type doubling patenting rejection over co-pending Application Serial No. 09/701,220, Applicants note that since this is a provisional rejection, Applicants will appropriately address the rejection once it is made non-provisionally upon the indication of allowable subject matter in both applications.

4. Rejections under 35 U.S.C. § 103

A. Claims 22, 32-33, 36-41, 55-61 and 64-74 are rejected under 35 U.S.C. § 103(a), allegedly, as obvious over EP 639373 (the '373 patent"), in combination with either U.S. Patent No. 5,049,388 to Knight *et al.* ("Knight"), or U.S. Patent No. 5,049,389 to Radhakrishnan ("Radhakrishnan"), or U.S. Patent No. 5,290,540 to Prince and Hemming ("Prince"); or *vice versa*. According to the Examiner, "[i]n the absence of showing unexpected results, it is deemed obvious to one of ordinary skill in the art to use an anti-septic agent and a wound healing promoting agent(encapsulated in liposomes) taught by [the '373 patent] to any part of the body including the respiratory tract . . ."

Applicants respectfully disagree with the Examiner's rejection. The currently pending claims are directed to methods of treating an infection in the lower respiratory tract by

administering liposomes containing povidone iodine. Such methods are not taught, much less suggested, by the references cited by the Examiner. Applicants submit that the rejection is improperly made since there is no suggestion for combining the references, especially in view of the fact that skin or eye tissue is not equivalent to the tissue found in the lower respiratory tract.

A rejection for obviousness is improper when there is nothing in the cited prior art references, either singly or in combination, to suggest the desirability of the claimed subject matter. For a rejection of claimed subject matter as obvious in view of a combination of prior art references to be upheld, (1) the prior art must have suggested to those of ordinary skill in the art that they should make the claimed composition or device or use the claimed method, as the case may be; and (2) the prior art must have revealed that in so doing, those of ordinary skill would have had a reasonable expectation of success. *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991); *In re Dow Chemical Co.*, 837 F.2d 469, 5 USPQ2d 1529 (Fed. Cir. 1988). The suggestion of the claimed invention must be in the prior art, not in the disclosure of the claimed invention. *In re Dow Chemical Co.*, 837 F.2d 469, 5 USPQ2d 1529 (Fed. Cir 1988). Moreover, identification in the prior art of each individual part claimed is insufficient to defeat patentability of the whole claimed invention. Rather to establish obviousness based on a combination of the elements disclosed in the prior art, there must be some motivation, suggestion or teaching of the desirability of making the specific combination that was made by the applicant. *In re Kotzab*, 217 F.3d 1365, 1370 (Fed. Cir. 2000). This showing of combinability must be "clear and particular". *In re Dembiczak*, 175 F.3d 994, 999; 50 U.S.P.Q.2d 1614, 1617 (Fed. Cir. 1999).

As has been discussed previously, the '373 patent teaches that liposomes containing povidone iodine can be used externally to treat infections, including in the eye. As admitted by the Examiner, the '373 patent provides absolutely no teaching for methods of treating an infection internally in the body, much less in the lower respiratory tract.

The disclosures of Knight, Radhakrishnan and Prince, which are interchangeable in the current analysis, do not fill in the gap between the '373 Patent and the claimed invention. All three references relate to the use of liposomal formulations, *inter alia*, for the treatment of lung diseases. None of these references teaches or suggests liposomes containing povidone iodine, much less that such povidone iodine-containing liposomes can be used in the methods of the invention for treating an infection in the lower respiratory tract. They merely teach that liposomes can be administered to the lung. These references do not teach or suggest that povidone iodine can be administered to the lung or lower respiratory tract. Since there is no

teaching or suggestion in the art for using liposomes containing iodine treat infections internally, the Examiner has not met the requirements for a *prima facie* rejection for obviousness.

Moreover, Applicants note that none of the substances taught by Knight, Radhakrishnan or Price to be administered to the lung in liposomes are similar to povidone iodine, which is an aggressive oxidizing antiseptic. Since none of the types of compounds disclosed by Knight, Radhakrishnan or Price are equivalent to the type of compound that is povidone iodine, no comparison can be made between the suitability to administer any of the compounds taught by Knight, Radhakrishnan or Price to administering povidone iodine. The Examiner merely alleges, without any substantiation, that the teaching in the '373 patent for applications to mucous membranes and the eye is "suggestive of the safe application of the compositions even for nasal oral or tracheal mucous tissues." However, this is mere speculation on the Examiner's part.

Further, the Examiner is directed to the Declaration of Dr. Wolfgang Fleischer under 37 C.F.R. § 1.132 ("Rule 132 Declaration"), in which Dr. Fleischer states that it is his belief that the compounds disclosed by the cited references are not comparable to povidone iodine and are not suggestive that povidone iodine could be administered safely to the lower respiratory tract (Rule 132 Declaration, § 5).

Applicants note that the Examiner is wrongly assuming that a compound applicable to the skin and eye is automatically applicable to the alveoli, bronchi and trachea of the lower respiratory tract. It is well known that lung tissue has a different function from, and is very different in structure from skin or eye or from any other mucous membrane, and that these tissues have different sensitivities to different agents. For example, the cells of the lower respiratory tract contain ciliated cells and specialized mucous secreting cells, and it is in the lower respiratory tract that gas exchange occurs. This lung tissue is highly sensitive and damaging such tissue can lead to severe illness, if not death. As evidence of the foregoing, the Examiner's attention is directed to Powell *et al.*, 2003, Chapter 18, Structure and Function of the Respiratory System, *in* Essential Medical Physiology, 3rd Edition, Leonard R. Johnson, Ed., Elsevier Academic Press, New York, pp. 259-276 ("Powell") which is attached as Exhibit A. Powell teaches the structure of the respiratory tract and the specialized cells in each part of the respiratory tract, as well as the respiratory and non-respiratory functions of the lung and sub-parts thereof. It is clear that these lung tissues are very different from skin, eye and the mucous membranes of the upper respiratory tract, including the nasal passages.

With regard to the Examiner's comment that the instant claims recite mercury containing compound and formaldehyde releasing compound, such compounds are no longer recited in the claims.

Applicants still believe that the Examiner is subconsciously using hindsight reconstruction and has simply combined prior art references without evidence of the required suggestion, teaching or motivation. The Federal Circuit has stated that the best defense against a hindsight-based obviousness analysis is rigorous application for the requirement for a showing of the teaching or motivation to combine the prior art references. *In re Dembiczak*, 175 F.3d 994, 50 U.S.P.Q.2d 1614 (Fed. Cir. 1999). In the instant application, Applicants submit that the Examiner has not provided the required suggestion, teaching or motivation to combine the teachings of the '373 patent with the teachings of Knight, Radhakrishnan or Prince since none the compounds taught in the cited art is suggestive of povidone iodine and since the tissues where povidone iodine has previously been applied are not suggestive of the tissues of the lower respiratory tract. Thus, Applicants respectfully submit that this Section 103 rejection is in error and must be withdrawn.

B. Claims 22, 32-33, 36-41, 55-61 and 64-74 are rejected under 35 U.S.C. § 103(a), allegedly, as obvious over EP 639373 (the '373 patent"), in combination with either U.S. Patent No. 5,049,388 to Knight *et al.* ("Knight"), or U.S. Patent No. 5,049,389 to Radhakrishnan ("Radhakrishnan"), or U.S. Patent No. 5,290,540 to Prince and Hemming ("Prince"); or *vice versa*, further in view of International Patent Publication WO 85/00112 ("International publication"). According to the Examiner, the International publication teaches the administration of vaporized povidone iodine to the nasal passages, and, thus, the International publication teaches that povidone iodine can be administered safely by inhalation, and thus, methods for treating an infection in the lower respiratory tract by administering liposomes containing povidone iodine are obvious. Applicants respectfully disagree.

The '373 patent, Knight, Radhakrishnan and Price are discussed above. Contrary to the Examiner's contention, the International publication teaches that microbiocidal agents, including povidone iodine, can be administered by inhalation of a stream or heated air containing the agents to the nasal passages only, which are in the upper respiratory tract. Applicants note that the heated air component is as an important part of the methods described in the International publication as are the microbiocidal agents. There is no indication that povidone iodine can be administered without heated air. Further, it is clear that the administration is only to the nasal passages, not to any other part of the respiratory tract, much less the lower respiratory tract.

There is no teaching or suggestion that liposomes containing povidone iodine can be administered to the lower respiratory tract to treat an infection. Since the nasal passages are a different tissue as compared to the tissue of the lower respiratory tract, application to the nasal passage is not suggestive of the lower respiratory tract. See the Rule 132 Declaration, § 6.

Therefore, for similar reasons as given above, the claimed methods are not rendered obvious by the '373 patent in combination with Knight, Radhakrishnan and Price, further in view of the International publication. Thus, Applicants respectfully request the withdrawal of this Section 103 rejection.

CONCLUSION

Applicants respectfully request that the above-made amendments and remarks of the present response be entered and made of record in the file history present application. Applicants submit that the presently pending claims meet all requirements for patentability and respectfully request allowance and action for issuance.

Applicants request that the Examiner call the undersigned at (212) 326-3921 if any questions or issues remain.

Respectfully submitted,

Date: September 10, 2004

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ESSENTIAL MEDICAL PHYSIOLOGY

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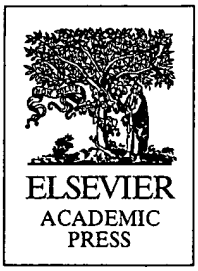

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CHAPTER

18

Structure and Function of the Respiratory System

FRANK L. POWELL, JR.

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KEY POINTS

- The primary function of the lung is *gas exchange*—transporting oxygen from the environment into the blood and eliminating carbon dioxide from the blood to meet the metabolic demands of the tissues.
- The lung is a series of branching tubes consisting of conducting airways (trachea to terminal bronchioles) and respiratory airways (respiratory bronchioles to alveoli).
- Transport of O_2 from small air sacs in the lung, called *alveoli*, into pulmonary capillary blood occurs by diffusion. The total surface area for diffusion in the lung is as large as a tennis court because there are 300 million alveoli.
- Quantitative descriptions of gas exchange depend on relatively simple applications of the principle of mass balance and the ideal gas law.
- *Ventilation* brings O_2 into the lungs by bulk flow. Total lung volume is more than 10 times larger than a normal breath, providing a large reserve capacity for increased ventilation.
- The pulmonary circulation is in series with the systemic circulation, so the lungs receive the entire cardiac output and pulmonary blood flow equals total systemic blood flow.
- In the pulmonary circulation, compared with the systemic circulation, pressures are lower,

KEY POINTS (*continued*)

the arterial-to-venous pressure drop is more uniform, and vessels have thinner walls.

- Vascular resistance and regional blood flow in the lungs are highly dependent on mechanical forces, including pressure inside the vessels, pressure around the vessels, and lung volume.
- Blood flow is greater in the bottom of the lungs than in the top, and gravity plays an important role in determining this distribution.
- *Hypoxia* is a potent vasoconstrictor in the lung and can divert blood flow to better ventilated regions of the lung.
- *Pulmonary edema* occurs when an imbalance in hydrostatic and colloid osmotic pressures across the capillaries produces more filtrate than can be removed by lymphatics.
- The lungs receive the entire cardiac output and serve important nonrespiratory functions, e.g., immune system defense and biosynthesis.

OVERVIEW OF THE RESPIRATORY SYSTEM

The primary function of the respiratory system is *gas exchange*—delivering oxygen (O_2) from the environment to the tissues and removing carbon dioxide (CO_2) from the tissues. Generally, the respiratory system acts as a servant to the rest of the body by delivering enough O_2 and removing sufficient CO_2 for metabolic demands. As O_2 demand increases, the body responds with a variety of mechanisms to ensure an adequate supply of O_2. These physiologic mechanisms include the unique functions of several cell types in the lung, pulmonary circulation, mechanics of the respiratory system, transport of O_2 and CO_2 in blood, respiratory gas exchange, and coordination of all of these mechanisms by the respiratory control system. Each of these topics is covered in subsequent chapters.

It is important that the respiratory system respond to changes in O_2 supply. Many of the responses to changes in O_2 supply are the same as those used to respond to changes in O_2 demand. If the supply-and-demand relationship for O_2 is disrupted by disease, then physical activity is limited and organ failure may occur. Diagnosing and treating respiratory disease requires understanding how the structure, function, and control of the respiratory system interact to match supply and demand at each step in the chain of O_2 transport.

Oxygen Cascade

Gas exchange between cells and the environment occurs by a series of physiologic transport steps across different structures, as shown in Fig. 1. (This figure uses a standard set of symbols developed for quantitative descriptions of respiratory physiology, which are defined in Table 1 and in the section titled "Physical and Chemical Principles in Respiratory Physiology.") Breathing movements bring fresh air into the lungs, and the heart pumps O_2-poor blood to the lungs. O_2 diffuses from the lung gas into the blood, and this O_2-rich blood is returned to the heart via the pulmonary circulation. Arterialized blood is pumped to the various organs and tissues of the body via the systemic circulation. Finally, O_2 diffuses out of the systemic capillaries to metabolizing tissues and ultimately to the mitochondria inside cells. CO_2 moves out of the cells to the environment through these same steps in the opposite direction from O_2. Figure 1 also shows normal values for the levels of O_2 and CO_2, expressed as partial pressures, P_{O_2}, and P_{CO_2} (see later discussion). Note that the O_2 level decreases at each step in this series of transport processes, so this transport chain is frequently called the *O_2 cascade*.

The physiologic principles governing O_2 supply-and-demand relationships can be studied by measuring maximal O_2 consumption while varying the supply. Figure 2 shows how decreasing oxygen levels in the

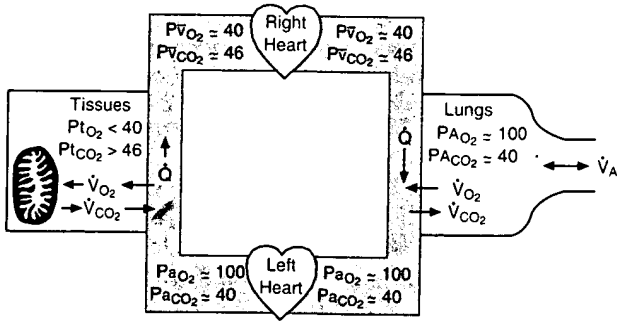

FIGURE 1 Oxygen uptake into the body ($\dot{V}_{O_2}$ in mL O_2/min) and carbon dioxide elimination ($\dot{V}_{CO_2}$ in mL CO_2/min) occur in a series of physiological transport steps from the atmosphere to mitochondria in the tissues. Typical O_2 and CO_2 partial pressures (P in mm Hg) are shown for gas in the alveoli of the lungs (A), arterial blood (a) and mixed-venous blood ($\bar{v}$) and tissues (t). $\dot{V}_A$, alveolar ventilation; $\dot{Q}$, blood flow rate. Symbols and units used in this section are defined in Table 1.

TABLE 1 Symbols in Respiratory Physiology

Primary Variables and Their Units	
C	Concentration or content (mL/dL or mmol/L)
D	Diffusing capacity (mL_{O_2}/(min. · mmHg)
F	Fractional concentration in dry gas (dimensionless)
P	Gas pressure or partial pressure (mmHg or cm H_2O)
$\dot{Q}$	Blood flow or perfusion (L/min)
R	Respiratory exchange ratio (dimensionless)
RQ	Respiratory quotient (dimensionless)
T	Temperature (°C)
V	Gas volume (L or mL)
$\dot{V}$	Ventilation (L/min)
Modifying Symbols	
A	Alveolar gas
B	Barometric
D	Dead space gas
E	Expired gas
$\bar{E}$	Mixed-expired gas
I	Inspired gas
L	Lung or transpulmonary
T	Tidal gas
aw	Airway
w	Chest wall
es	Esophageal
pl	Intrapleural
rs	Transrespiratory system (total system)
a	Arterial blood
b	Blood (general)
c	Capillary blood
c′	End-capillary blood
t	Tissue
v	Venous blood
$\bar{v}$	Mixed-venous blood
Examples	
P_{AO_2}	Partial pressure of O_2 in alveolar gas
Pa_{O_2}	Partial pressure of O_2 in arterial blood
F_{E-CO_2}	Fraction of CO_2 in dry mixed, expired gas
$\dot{V}_{O_2}$	O_2 consumption per unit time
$\dot{V}_A$	Ventilation of the alveoli per unit time

environment affect maximal O_2 consumption, equivalent to the maximum capacity for aerobic exercise in a healthy individual. Maximal O_2 consumption for the whole body starts to decrease at relatively high levels of O_2, in comparison with mitochondria. Isolated mitochondria can continue to function until O_2 levels decrease to almost zero, whereas whole-body O_2 consumption is limited when environmental O_2 decreases only 25%. This is not an artifact of the *in vitro* methods used to measure mitochondrial O_2 consumption, but a consequence of the decrease in O_2 levels occurring at each step in the O_2 transport chain. A healthy respiratory system functions to preserve high O_2 levels at each step in the transport chain.

Interface between the Respiratory System and the Environment

High O_2 levels are desirable in the respiratory system because O_2 transport ultimately occurs by passive diffusion down an O_2 gradient. Ventilatory and cardiovascular pumps are used to deliver O_2 by bulk flow in air or blood to large surface areas, where diffusion of O_2 can occur. The actual interface between the environment and the body's *internal milieu* occurs deep in the lungs at the pulmonary blood–gas barrier. Figure 3A illustrates the branching pattern of airways used to deliver gas to the terminal lung units called *alveoli*. The trachea divides into two smaller primary bronchi to each lung, and the primary bronchi divide into still smaller bronchi to the different lobes of the lung. The pulmonary blood vessels undergo a similar branching pattern so the alveoli are virtually covered with pulmonary capillaries (Fig. 3B).

The effect of this branching is to increase greatly the surface area available for gas exchange by diffusion. If the lungs were two simple spheres of about 3 L each, they would have a total internal surface area of only 0.1 m^2. However, the lungs branch more than 20 times, so the lungs contain more than 300 million alveoli of only about 300 μm in diameter. The surface-to-volume ratio increases as the diameter of a sphere decreases, so dividing the large volume of the lung into millions of smaller units results in an extremely large area available for gas exchange. The total surface area of the lung's blood–gas barrier is 50–100 m^2, or about the area of a tennis court!

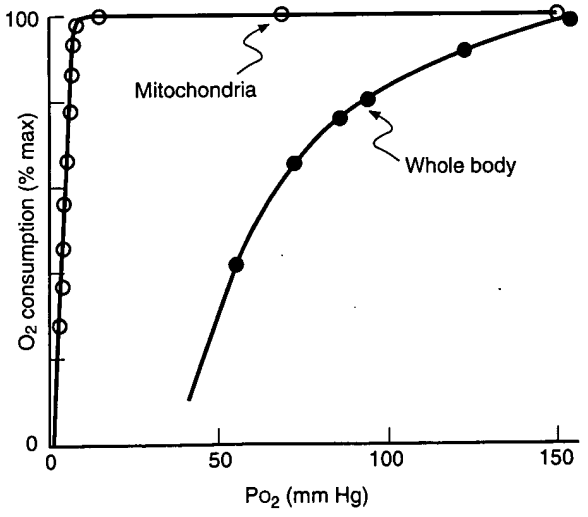

FIGURE 2 Maximal O_2 consumption is less sensitive to decreased O_2 supply in isolated mitochondria than in the whole body, because O_2 levels decrease between the environment and the mitochondria. P_{O_2} is a measure of O_2 level in mitochondrial suspension medium or inspired air. (After Winzler, *J Cell Comp Physiol* 1941;17:263, and Pugh *et al.*, *J Appl Physiol* 1964;19:431.)

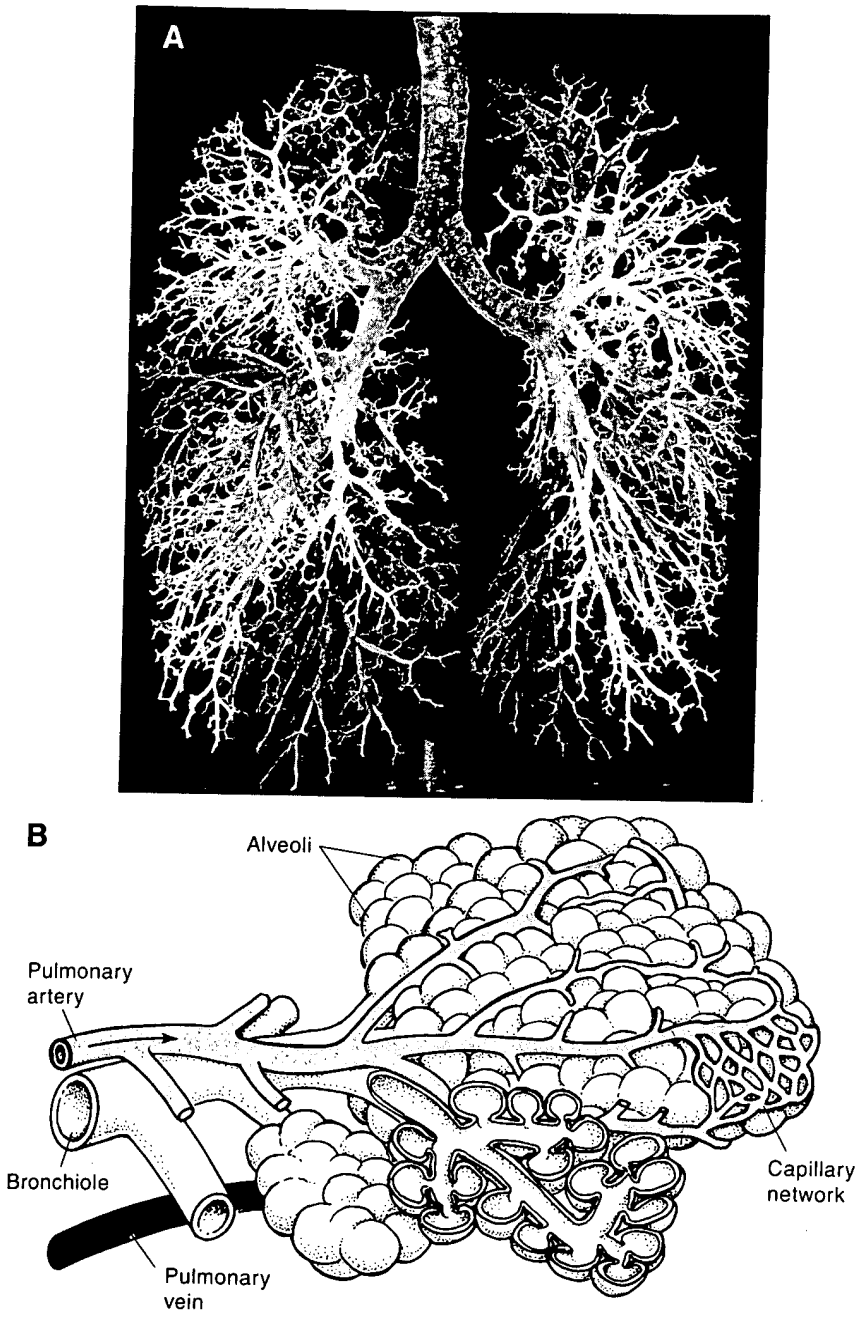

FIGURE 3 (A) Plastic cast of the lung airways showing extensive branching. (B) Diagram of terminal airway branches in an acinus, which is the functional unit of gas exchange in the lung. Pulmonary arterioles travel next to the bronchi to the level of respiratory bronchioles and branch extensively to cover the alveoli with pulmonary capillaries. Pulmonary veins are further from the bronchioles.

Physical and Chemical Principles in Respiratory Physiology

Quantitative descriptions of gas exchange depend on relatively simple applications of the principle of conservation of mass (or mass balance) and the ideal gas law using the symbols defined in Table 1. The symbols may appear complicated at first, but they are based on a few simple conventions. *Primary variables* are symbolized with a *capital letter*, and a *dot* over the variable indicates the *first derivative with respect to time* (e.g., $\dot{Q}$ = blood flow, or quantity of blood per unit time in liters per minute). *Modifiers are small capitals for the gas phase* (e.g., $\dot{V}_A$ = alveolar ventilation) and *lowercase letters for*

liquid or tissues (e.g., Pa = partial pressure in arterial blood). Finally, a specific *gas species* is indicated with a *subscript* (eg, C_{AO_2} = O_2 concentration in arterial blood in mL O_2/dL blood).

The principle of *conservation of mass* is simply that matter is neither created nor destroyed. This principle was applied to physiologic transport by the German physiologist Fick in the last century. The *Fick principle* states that the amount of a substance consumed or produced by an organ is the difference between the amount of the substance entering the organ and the amount leaving the organ. To calculate whole-body O_2 consumption ($\dot{V}_{O_2}$ in milliliters per minute), one measures the difference between the amount of O_2 inspired and the amount of O_2 expired from the lungs per unit time. The amount of O_2 inspired = $\dot{V} \cdot F_{IO_2}$, where $\dot{V}$ = ventilation (in liters per minute) and F_{IO_2} = fractional concentration of O_2 in inspired gas (0.21 for room air). The amount of O_2 expired = $\dot{V} \cdot F_{EO_2}$, where F_{EO_2} is the fractional concentration of O_2 in mixed-expired gas. If inspired ventilation equals expired ventilation, then:

$$\dot{V}_{O_2} = \dot{V}_E(F_{IO_2} - F_{EO_2}).$$

In a steady state, $\dot{V}_{O_2}$ is equal at each of the steps in the O_2 cascade, so a similar equation can be written for the cardiovascular system. The amount of O_2 consumed by the body equals the difference between arterial O_2 delivery and venous O_2 return:

$$\dot{V}_{O_2} = \dot{Q}(C_{aO_2} - C\bar{v}_{O_2}),$$

where $\dot{Q}$ = cardiac output (in liters per minute), C_{aO_2} = O_2 concentration in arterial blood (mL O_2/dL blood), and $C\bar{v}_{O_2}$ = O_2 concentration in mixed venous blood. The Fick principle can be used to calculate cardiac output ($\dot{Q}$) from measurements of whole-body O_2 consumption and arterial and venous O_2 concentrations by rearranging the preceding equation.

Chapter 21 considers more applications of the Fick principle, which describes gas transport by *convection*, or *bulk flow* of air or blood. In contrast, *diffusion* is the mechanism of O_2 transport across the blood–gas interface in the lungs and across systemic capillaries in metabolizing tissues. Fick also quantified diffusive gas transport with *Fick's first law of diffusion:*

$$\dot{V}_{O_2} = \Delta P_{O_2} D,$$

where ΔP_{O_2} is the average O_2 partial pressure gradient between two compartments, and D is a diffusing capacity, as defined in Chapter 21.

Note that the diffusive transport of respiratory gases occurs down a partial pressure gradient. *Partial pressure* of a gas is defined by *Dalton's law,* which states that the partial pressure of gas x in a mixture of gases is equal to the pressure that gas x would exert if the other gases were not present. Therefore:

$$P_x = F_x(P_{tot}),$$

where F_x is the fractional concentration of gas x in a *dry* gas sample. For example, P_{O_2} in dry air at sea level is 160 mm Hg (= 0.21 · 760 mm Hg, where the O_2 concentration is 21% in air and barometric pressure is 760 mm Hg at sea level). Partial pressure is also expressed in units of Torr (1 Torr = 1 mm Hg) or SI units of kilopascals (1 kPa = 7.5 mm Hg) in physiology.

For calculating partial pressure in the gas phase, it is important to specify the total *dry* gas pressure because of the effects of water vapor pressure in humidified gases. *Water vapor pressure* is determined only by the temperature and relative humidity of a gas, and it is independent of total pressure. Inside the lungs, temperature is generally 37°C and relative humidity is 100%. Saturated water vapor pressure at 37°C = 47 mm Hg, so the total gas pressure available for O_2 and CO_2 inside the body is reduced by this amount. Assuming barometric pressure equals 760 mm Hg:

$$P_{dry} = (760 - 47) = 713 \text{ mmHg}.$$

Therefore, P_{O_2} in inspired gas, which is saturated with water vapor at body temperature, is only 150 mm Hg (= 0.21 · 713 mm Hg) at sea level.

Gases dissolved in fluids also exert a partial pressure, and diffusion of gases also occurs down partial pressure gradients between fluids. For example, O_2 diffuses from O_2-rich blood in capillaries toward mitochondria where it is near zero. The partial pressure of gas x in solution equals P_x in a gas mixture that would be in equilibrium with that solution. *Henry's law* describes the linear relationship between the concentration (C in mL/dL or mmol/L) and partial pressure (P in mm Hg) of gas x dissolved in solution:

$$C_x = \alpha_x P_x,$$

where α_x is the physical *solubility* of gas x in the solution. The relationship between O_2 and CO_2 concentration and partial pressure in blood is more complex because of chemical reactions between these physiologic gases and blood (Chapter 20).

The volume of a gas sample depends on temperature and pressure according to the *ideal gas law:*

$$PV = nRT,$$

where n is the number of moles, R is the universal gas constant, and T is temperature in degrees kelvins. *Avogadro's law* specifies that 1 mol of an ideal gas occupies 22.4 L at standard temperature (0°C) and standard pressure (760 mm Hg) when dry. Such volumes are called *standard temperature and pressure dry* (STPD), and can be used instead of moles to quantify the amount of a gas. For example, $\dot{V}O_2$ and $\dot{V}CO_2$ are generally expressed as mL$_{STPD}$/min.

Ventilation and lung volumes are not usually dry gas volumes measured at 0°C and 760 mm Hg, however. Lung volumes occur at body temperature, actual barometric pressure, and saturated with water vapor. Such physiologic volumes are called *body temperature and pressure saturated* (BTPS) and they can be converted to STPD volumes as follows:

$$V_{STPD} = V_{BTPS}\,(273\text{ K}/T_{BODY}\text{ in K})\,(P_B/760)\,([P_B - P_{H_2O}]/P_B).$$

At 37°C and P_B = 760 mm Hg, this simplifies to:

$$V_{STPD} = V_{BTPS}\,(273°/310°)\,(713/760)$$
$$V_{STPD} = V_{BTPS}\,(0.826).$$

This equation derives from two special applications of the ideal gas law. *Boyle's law* states that volume is inversely proportional to pressure at constant temperature:

$$V_1/V_2 = P_2/P_1.$$

Charles' law states that volume is directly proportional to temperature at constant pressure:

$$V_1/V_2 = T_1/T_2.$$

Volumes are measured frequently at ambient temperature and pressure, or *ambient temperature and pressure saturated* (ATPS) conditions. For normal values of P_B = 760 mm Hg and T = 37°C, ATPS can be converted to STPD or BTPS by:

$$V_{STPD} = V_{ATPS}\,(0.885)$$
$$V_{BTPS} = V_{ATPS}\,(1.086).$$

LUNG AIRWAYS AND VENTILATION

Airways

The lung is a series of branching tubes leading from the *trachea* to small terminal air sacs at the ends of the airways called *alveoli*. At each branch point in this tree, the daughter branches are smaller in diameter but there are at least two more of them. For example, the single trachea divides into two slightly smaller main stem (or primary) bronchi to the right and left lungs. Figure 4 shows the types of airways in the 23 orders of bronchial branching that occur in a human lung. Note that all bronchi beyond the 16th generation contain some alveoli, so the number of alveoli (300 million) is even greater than the number predicted for one at the end of each branch in a tree with 23 bifurcations (2^{23}; 8.4 million). Although each airway generation is smaller, their number is increasing exponentially so the total cross-sectional area of the airways increases dramatically with each generation. The total cross-sectional area of the first 10 generations of airways is relatively constant at a few square centimeters. However, by the 17th generation, the total cross-sectional area of the airways is more than 200 cm^2.

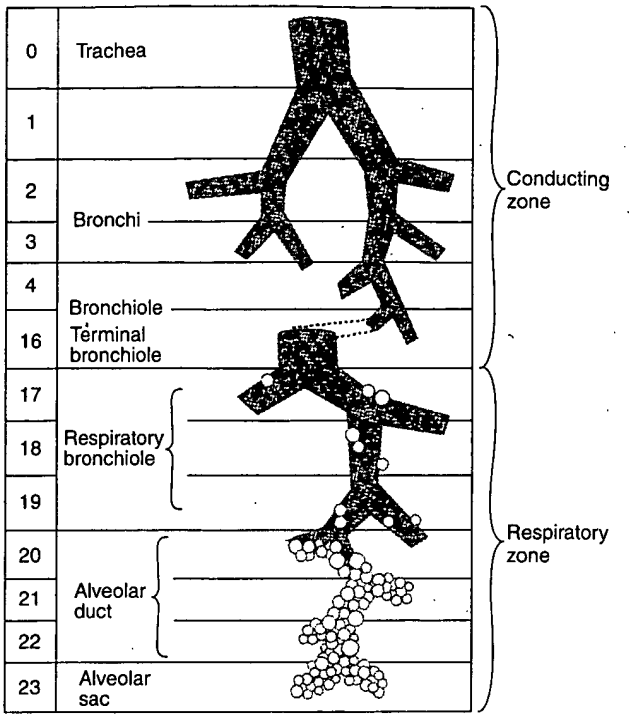

FIGURE 4 The airway tree consists of two functional zones: The conducting zone includes the first 16 orders of branching and does not participate in gas exchange; the respiratory zone includes the last 7 orders of bronchial branching, which have alveoli that are responsible for gas exchange. (After Weibel, *Morphometry of the human lung*. Berlin: Springer, 1963.)

This dramatic increase in cross-sectional area has an important functional consequence for gas exchange. Once the total area is large enough, and the distances to the gas exchanging airways are short enough, the forward velocity of bulk flow decreases and diffusion becomes an effective mechanism for gas transport. Hence, diffusion is the primary mechanism of gas transport in airways after the terminal bronchioles. The airways and alveoli served by a terminal bronchiole

are called an *acinus* (Fig. 3B). There are about 150,000 acini, with a path length for gas transport of about 5 mm in human lungs. The acinus is the functional unit of gas exchange because diffusion is so effective at mixing and equilibrating gas in it.

Figure 4 shows how the airways can be divided into a *conducting zone* and a *respiratory zone*. Airways in the respiratory zone are structurally stronger and function to distribute air by convection to peripheral airways. There is no significant uptake of O_2 or elimination of CO_2 across the walls of conducting airways. The respiratory zone consists of peripheral airways that function to equilibrate blood with lung gases, and this zone contains most of the lung volume. Airways and alveoli in the respiratory zone can be extremely delicate to facilitate diffusion from lung gas to blood because they are not subject to the larger stresses associated with ventilation and bulk flow.

Figure 5 shows how the structure and cellular biology of the airways change between the conducting and respiratory zones. These changes involve three principles of organization: (1) The airways form a barrier between gas and the body consisting of *layers* of epithelium, interstitium, and endothelium; (2) airway cells are *differentiated* according to their hierarchy in the tree of bronchial branching; and (3) a *mosaic* of airway cell types changes between the conducting and airway zones.

In the trachea and large bronchi, the airway walls are very thick and include *cartilage* and smooth muscle to provide structural support. The airway *epithelial cells* form a confluent (or continuous) sheet that is anchored by *basement membrane* and covers the entire internal surface of the airways, from the trachea to the alveoli. *Tight junctions* between epithelial cells limit and control molecular transport across this barrier. The mosaic of *columnar* epithelial cells in the bronchi includes *ciliated cells* and superficial *Goblet cells* that secrete mucous glands. Other mucous cells form invaginations in the airway that function as submucosal secretory glands. The surface cilia move secreted mucus toward the mouth to remove foreign objects from the airways. Neuroendocrine cells that secrete mediators into the bloodstream are relatively rare. Endothelial cells in the bronchi are part of the systemic circulation, which supplies the nutrient demands of large airways by the bronchial circulation.

In the transition zone, there is no cartilage, but helical bands of *bronchial smooth muscle* surround the airways. This smooth muscle controls bronchial caliber, airway resistance, and the local distribution of ventilatory gas flow. Ciliated epithelial cells are smaller and *cuboidal* in the transition zone. Goblet cells on the airway surface secrete mucus to be moved up and out of the airways by the ciliated epithelial cells. *Clara cells* are another type

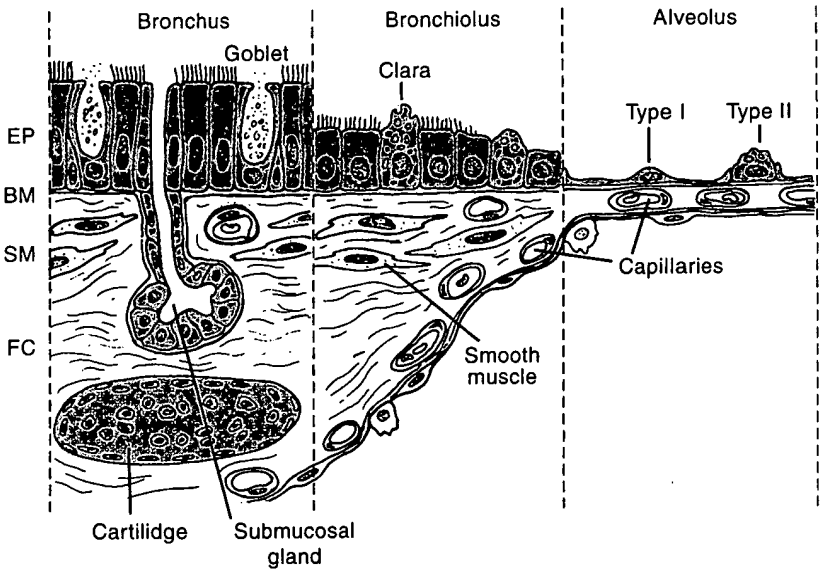

FIGURE 5 Cellular structure of airways showing how the layering and cellular forms at different levels from the trachea (left) to the alveoli (right). Both nonciliated epithelial cells (goblet cells) and submucosal glands secrete mucus in the bronchi. Secretory Clara cells occur in the bronchioles. The alveoli do not contain cilia but do contain type II epithelial cells that secrete surfactant. The epithelium (EP), basement membrane (BM), and interstitium (IN) are very thin in the alveoli to allow effective diffusion of O_2 from alveolar gas through pulmonary capillary endothelium and into blood. (After Burri and Weibel, *Rontgendiagnostik der lunge*, Huber, 1973.)

of secretory epithelial cell in the small bronchi but their function is not known.

In the respiratory zone, there is no smooth muscle and little connective tissue. *Type I alveolar epithelial cells* are *squamous* (or flattened), with long and thin cytoplasmic extensions and no cilia so the epithelial barrier to gas exchange is as thin as possible. The interstitial layer and pulmonary capillary endothelial cells are also very thin, reducing the barrier to gas exchange. *Type II alveolar epithelial cells* are specialized cells that synthesize and secrete surfactant, a substance that influences the mechanical properties of the lung, as described in Chapter 19. Type II cells are also precursors for type I cells and important for repair in lung injury.

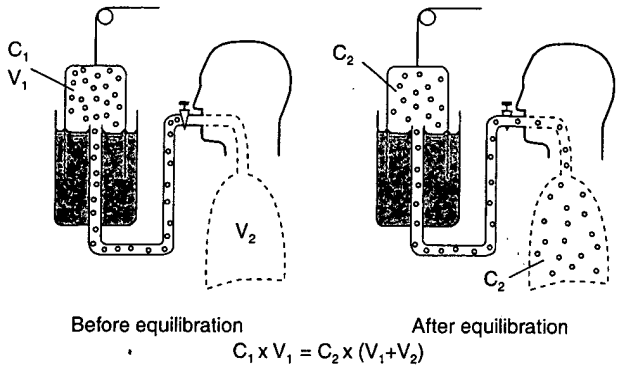

FIGURE 7 Measurement of FRC by helium dilution as described in the text. V_1, spirometer volume; V_2, FRC; C_1, initial helium concentration; C_2, final helium concentration.

Lung Volumes

The volume of gas in the lungs can be divided into different components, and these individual volumes can be useful in diagnosing certain pulmonary diseases. Figure 6 shows the different volumes that can be measured with a spirometer. A *spirometer* measures the volume inspired or expired by a subject through a mouthpiece connected to a container with a water seal (as in Fig. 6) or a collapsible bellows (which is more common today). The patient wears a nose clip to ensure that an entire inhalation or exhalation is collected.

Total lung capacity (TLC) is the maximum volume that can be contained by the lungs *in vivo*, and it includes several different volumes. The convention is that *capacities are composed of volumes* that can be measured independently. *Residual volume* (RV) is the one volume that cannot be measured with a spirometer because it is the volume of gas remaining in the lungs after a maximal expiratory effort. Therefore, absolute values of TLC and the *functional reserve capacity* (FRC) cannot be measured with a spirometer. FRC is the volume of gas left in the lungs at the end of a normal passive expiration.

Tidal volume (V_T) is the normal volume inspired and expired with each breath. *Inspiratory reserve volume* (IRV) is the maximum volume that can be inspired above the end of a normal inspiration, and the *expiratory reserve volume* (ERV) is the maximum volume that can be forcibly exhaled after a normal expiration (i.e., below FRC). *Inspiratory capacity* (IC) is the maximum volume that can be inspired from FRC and the *vital capacity* (VC) is the maximum volume that can be inhaled or exhaled *in vivo*.

One method used to measure RV or FRC is that of gas dilution, which is another application of the principle of conservation of mass as illustrated in Fig. 7. The initial

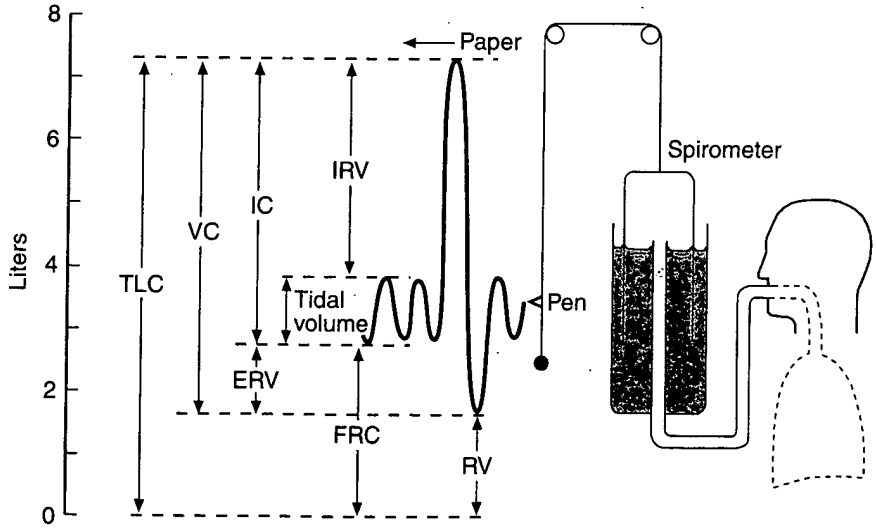

FIGURE 6 Only lung volumes that do not include residual volume (RV) can be measured with a spirometer. TLC, total lung capacity; VC, vital capacity; IC, inspiratory capacity; ERV, expiratory reserve volume; IRV, inspiratory reserve volume; FRC, functional reserve capacity.

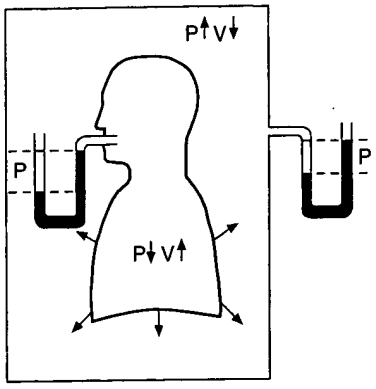

FIGURE 8 Measurement of FRC with a body plethysmograph. Pressure (P) and volume (V) changes measured when the subject attempts to inspire against a closed airway are used to calculate lung volume as described in the text ($P \cdot V = k$).

lung volume (V_2), which can be FRC or RV, contains none of a tracer gas such as helium. After the mouthpiece is opened to the spirometer, the individual rebreathes in and out of the spirometer until the tracer gas concentration equilibrates in the lung volume and the spirometer. O_2 can be added to the spirometer to replace that consumed and CO_2 can be removed by CO_2 absorbents. If the final tracer gas concentration (C_2) is measured, and the initial spirometer volume (V_1) and tracer gas concentration (C_1) are known, then one can solve for the unknown lung volume (V_2).

Another method used to measure FRC is that of a body *plethysmograph* as illustrated in Fig. 8. A plethysmograph is a sealed box in which an individual can sit and breathe through a mouthpiece connected outside the box. The mouthpiece is sealed at a specified lung volume, such as FRC, and the person makes an inspiratory effort. First, Boyle's law is used to calculate the change in box volume (ΔV) from the known initial box volume (V_1) and pressure (P_1), and the final box pressure (P_2) measured during inspiratory effort:

$$P_1V_1 = P_2(V_1 - \Delta V).$$

Next, Boyle's law is applied to the lung where FRC is the unknown initial lung volume and P_3 and P_4 are the initial and final lung pressures measured at the mouth:

$$P_3\text{FRC} = P_4(\text{FRC} + \Delta V).$$

The decrease in box volume equals the increase in lung volume (ΔV), and the equation can be solved for FRC.

The measurement of lung volumes can be a useful diagnostic tool for pulmonary disease. For example, FRC increases with emphysema or chronic obstructive lung disease. However, the methods for measuring lung volumes can also be affected by disease. Gas dilution depends on the tracer gas reaching all parts of the lung volume, which may not occur with lung disease and gas trapping in obstructed distal airways. In contrast, the plethysmograph method will also measure trapped gas volumes within the thorax.

Normal lung volumes also provide important lessons about respiratory physiology in healthy individuals. TLC is more than 10 times larger than the normal V_T, so there is a tremendous reserve capacity for increased ventilation with increased O_2 demand or reduced supply. This is part of the reason why pulmonary gas exchange is usually not a limiting factor in O_2 uptake at sea level in anyone except highly trained elite athletes. It is also important that the FRC is over three times larger than normal V_T. Ventilation is tidal (i.e., in and out), so oscillations in alveolar gas composition can occur during the breathing cycle. However, the large FRC relative to V_T dilutes these oscillations in alveolar gas composition so P_{O_2} and P_{CO_2} in blood leaving the pulmonary capillaries is almost constant (±2–4 mm Hg).

Ventilation

Ventilation is defined as the volume of air moved into or out of the lungs in a given time, and it can be changed by changing either the volume of a breath (V_T) or the *respiratory frequency* (f_R). In an average healthy human, V_T is about 500 mL and f_R is about 12 breaths/min, so *expired ventilation* ($\dot{V}_E$) is about 6 LBTPS/min (= 0.5 L/breath · 12 breaths/min). If either V_T or f_R are doubled, then $\dot{V}_E$ will double. Similar reductions in f_R or V_T also have equivalent effects on $\dot{V}_E$.

Because ventilation is a tidal process and the conducting airways do not participate in gas exchange, not all of the inspired volume is effective at gas exchange. Figure 9 shows that only a part of V_T is

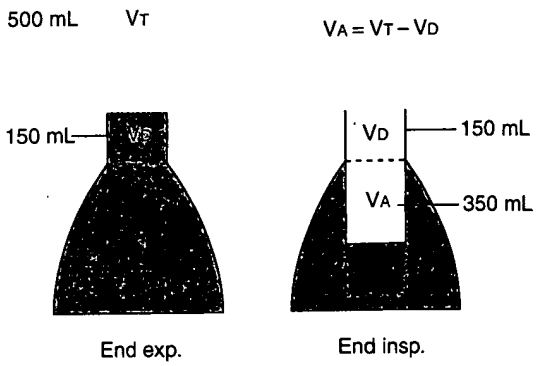

FIGURE 9 Tidal volume (V_T) includes a volume that reaches the alveoli and is effective at gas exchange ($\dot{V}_A$), and dead space volume that remains in the conducting airways and is not effective at gas exchange (V_D).

effective at bringing fresh gas to the alveoli because (1) the first gas inspired is gas left in conducting airways from the last expiration, which has already had O_2 removed and CO_2 added to it in the lungs; and (2) the last part of an inhalation does not get past the conducting airways and into the gas exchanging alveoli. The volume in the conducting airways that is not effective at gas exchange is called *anatomic dead space* (V_D). The portion of ventilation effective for gas exchange is that portion actually reaching the alveoli, or alveolar ventilation ($\dot{V}_A$). In a normal individual, anatomic V_D is about 150 mL (or about 1 mL/lb body mass) so $\dot{V}_A$ is only about 4.2 L/min:

$$\dot{V}_A = f_R(V_T - V_D).$$

The effects of changing f_R on $\dot{V}_A$ are different from those of changing V_T, in contrast to the case for $\dot{V}_E$. Doubling or halving f_R will double or halve $\dot{V}_A$, respectively. However, doubling V_T will more than double $\dot{V}_A$ if V_D is constant. Similarly, decreasing V_T can decrease $\dot{V}_A$ disproportionately. Differential effects of V_T and f_R on $\dot{V}_A$ have important implications for artificial ventilation. It also means that the optimal breathing pattern depends on gas exchange, in addition to respiratory mechanics.

Anatomic dead space can be measured with a *single breath method* as shown in Fig. 10. Nitrogen concentration is continuously measured at the mouth of a person who inspires a breath of pure O_2, and then slowly exhales to RV. Expired volume is measured at the same time. The first gas expired from the dead space contains the pure O_2 that was just inhaled. After the dead space gas, alveolar gas that still contains nitrogen is expired. There is not a perfectly sharp transition between the anatomic dead space gas and alveolar gas because of diffusive mixing at the interface between conducting and respiratory airway zones. However, the average volume at this interface can be determined as shown in Fig. 10, and this equals the anatomic dead space volume.

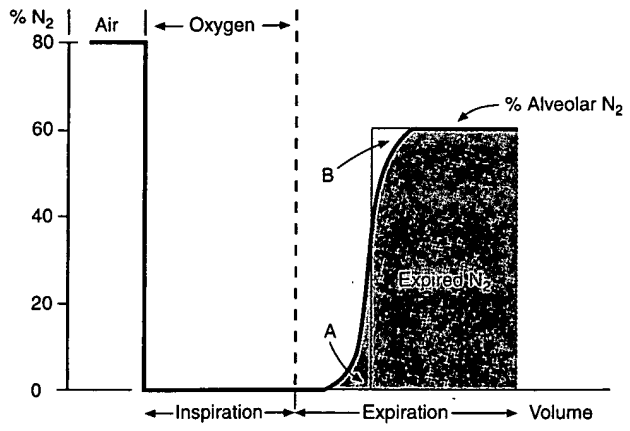

FIGURE 10 Fowler's method for measuring dead space as described in the text. After a single inspiration of 100% O_2, expired N_2 concentration is plotted against expired volume. A vertical line drawn so area A = area B, and this line intersects the volume axis at the anatomic deadspace volume (V_D). In real life, the alveolar plateau may slope and have inflection points from uneven ventilation between lung regions (see Chapter 21).

In reality, anatomic V_D can increase with V_T as conducting airways lengthen and dilate during inspiration, and vice versa during expiration. Also, as discussed in Chapter 21, $\dot{V}_A$ may be reduced even more by *physiologic dead space,* which can exceed anatomic dead space.

PULMONARY CIRCULATION

There are important differences in structure and function between the pulmonary and systemic circulations. The first difference involves the correct use of the words *arteries* and *veins* as delivery and return vessels, respectively. Arteries and veins cannot be defined by the O_2 content of the blood they contain. Systemic venous blood returns to the right atrium of the heart, and the right ventricle pumps this deoxygenated blood to the lungs through the *pulmonary arteries*. Oxygenated blood from the pulmonary capillaries flows into the *pulmonary veins*. The pulmonary veins return blood to the left atrium and the left ventricle pumps blood through the systemic circulation again.

Another important difference is that the lung is the only organ to receive the entire *cardiac output*. Because the amount of blood pumped by the right and left ventricles is equal, and because the pulmonary and systemic circulation are in series, the lungs receive the same amount of blood flow as the rest of the body. This places the lung in a unique position to process blood. Also, many of the structure–function relationships in the pulmonary circulation are explained by the fact that the lungs must handle high rates of blood flow.

Bronchial Circulation

The *bronchial circulation* is part of the systemic circulation, and it serves the metabolic needs of the large airways and blood vessels. The bronchial circulation does not extend to the respiratory zone, which is served by the pulmonary circulation. Bronchial arteries arise from the aorta and intercostal arteries, and the bronchial circulation returns blood to the heart by two pathways. Bronchial veins from large airways return about half the bronchial blood flow to the right heart via the azygos vein. The other half of the bronchial circulation drains directly into the *pulmonary*

circulation. This adds deoxygenated blood to the oxygenated blood returning to the left heart, and constitutes an *anatomic shunt*. Blood flow through the bronchial circulation is only 1–2% of cardiac output in normal individuals, so this anatomic shunt has a small effect on arterial O_2 levels. However, the anatomic shunt can increase with inflammatory airway disease and cause significant reductions in arterial O_2 levels.

Pulmonary Vascular Pressures

Table II shows that the pressures in the pulmonary circulation are generally lower than in the systemic circulation, for at least two reasons. First, the pulmonary circulation supplies only a single organ, so a large pressure head is not necessary to distribute blood flow to multiple organs at different distances from the heart. The right ventricle only needs to generate sufficient pulmonary artery pressure to lift blood to the top of the lung. Low pressures mean that the pulmonary artery and its branches can have relatively thin walls, and they have much less connective tissue and smooth muscle compared with systemic arteries and arterioles. Pulmonary vascular pressures are so low that they are often measured with units of cm H_2O, instead of mm Hg (1.3 cm H_2O = 1 mm Hg). Second, *pulmonary capillaries* are not supported on the outside by tissue. Pulmonary capillaries are exposed to open gas spaces in the alveoli, so they are more susceptible than systemic capillaries to *stress failure,* or bursting open if their internal hydrostatic pressure is too high. All capillaries must be extremely thin to allow effective diffusion of gases.

Table II also shows that the pressure drop from artery to vein is more uniform in the pulmonary circulation than in the systemic circulation. Direct and indirect measurements indicate that pulmonary capillary pressure is near the mean of the average pulmonary arterial and venous pressures. Pulmonary capillaries contribute to more of the total pressure drop from artery to vein than do systemic capillaries. This means that capillaries are more important determinants of total resistance in the pulmonary circulation, compared with the systemic circulation.

Pulmonary vascular pressures can be altered by a variety of physiologic and pathologic conditions. For example, mean pulmonary artery pressure can increase to more than 35 mm Hg during exercise, and pulmonary venous pressure can exceed 25 mm Hg in patients with congestive heart failure. Pressures in the pulmonary circulation also vary a small amount with the ventilatory cycle. This is because the heart is surrounded by intrapleural pressure, which decreases on inspiration and increases on expiration (Chapter 19). Consequently, vascular pressures tend to fall on inspiration.

TABLE II Mean (or Systolic/Diastolic) Pressures in the Pulmonary and Systemic Circulations (mm Hg)

	Pulmonary	Systemic
Ventricle	Right (25/0)	Left (120/80)
Artery	15 (25/8)	100 (120/80)
Arteriole	12	30
Capillary	10	20
Venule	8	10
Atrium	Left 5	Right 2

Pulmonary Vascular Resistance

The hydraulic analogy of *Ohm's law* can be used to define the relationship between pulmonary vascular pressure, flow, and resistance:

$$\Delta P = \dot{Q} \cdot \text{PVR},$$

where ΔP is the pressure gradient between the inlet and outlet of a vessel (in mm Hg or cm H_2O), $\dot{Q}$ is blood flow (in liters per minutes), and PVR is *pulmonary vascular resistance*. PVR is by definition the resistance for both lungs and is about 1.7 (mm Hg · min)/L for a normal cardiac output of 6 L/min with an average pressure drop of 10 mm Hg from the pulmonary artery to left atrium.

The resistance to flow through a vessel obviously depends on its dimensions. The dimensions of pulmonary vessels are strongly influenced by several external forces, which is different from the situation for rigid pipes in a plumbing system, or even systemic arteries. The fundamental geometry of the pulmonary capillary network is also different from pipes or systemic capillaries, as illustrated in Fig. 11. The numerous capillaries in the alveolar wall constitute an almost continuous sheet for blood flow between two flat membranes held together by numerous posts. This is called *sheet flow,* and the resistance to sheet flow can be less than the resistance to flow through a network of tubes. Therefore, Poiseuille's law (Chapter 19) cannot be used to calculate pulmonary capillary resistance from capillary dimensions. Still, PVR increases with the length and decreases by a power function with the internal size of pulmonary capillaries.

The primary determinant of vessel size is the *transmural pressure,* which depends on the pressure difference between the inside and outside of the vessel:

$$P_{\text{transmural}} = P_{\text{inside}} - P_{\text{outside}}.$$

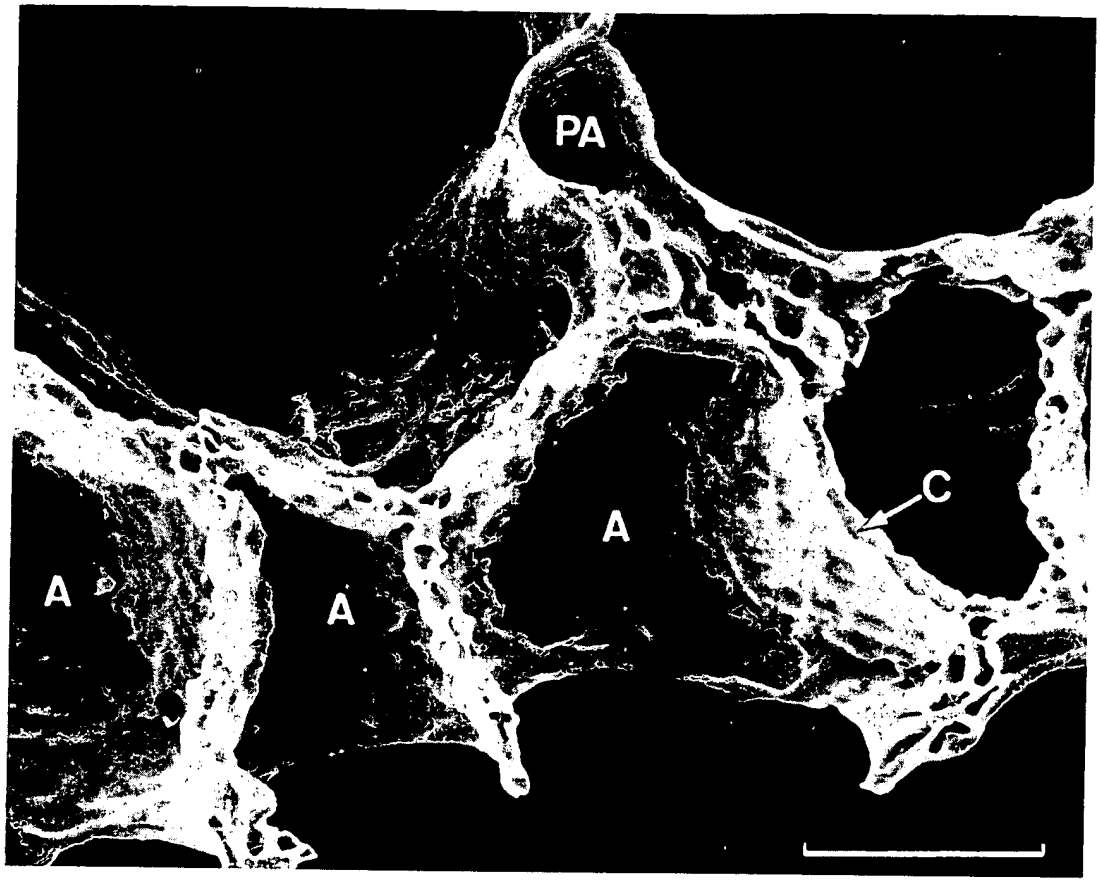

FIGURE 11 Blood flow in pulmonary capillaries (C) surrounds the alveoli (A) like a "sheet" of blood flow. PA, pulmonary arteriole; marker = 50 μm. (From Weibel, Chap. 82 in Crystal *et al.*, eds., *The lung: Scientific foundations*. Philadelphia: Lippincott-Raven, 1997.)

Therefore, increasing pulmonary arterial pressure will increase flow by two mechanisms: (1) the pressure gradient for Ohm's law is increased and (2) the transmural pressure is increased, which increases vessel size and decreases PVR. Figure 12 shows how PVR becomes even smaller when pulmonary arterial pressure is increased. Increasing pulmonary venous pressure also decreases PVR, because some of this pressure increase is transmitted to the capillaries. As discussed earlier, capillary dimensions significantly affect PVR. Hence, pressure affects resistance and vice versa in the pulmonary circulation, in contrast to the systemic circulation in which resistance primarily affects pressure.

Alveolar pressure is the outside pressure for calculating transmural pressure in most pulmonary vessels. Alveolar pressure varies with the ventilatory cycle, but it is generally near zero (i.e., atmospheric pressure; see Chapter 19). Therefore, vascular pressure is the primary determinant of transmural pressure in pulmonary vessels. However, large positive alveolar pressures can occur with some forms of artificial ventilation, and this will tend to collapse pulmonary capillaries.

Increasing transmural pressure can affect capillary dimensions by two mechanisms: *recruitment* and *distention*. At very low pressures, some capillaries may be closed, and increasing pressure will open them by recruitment. At higher pressures, capillaries are already open, but they may be distended or stretched by increased transmural pressure. Together, recruitment and distention increase the effective size of the pulmonary capillaries and reduce PVR.

Another important determinant of pulmonary vessel size is lung volume, but this effect differs for different types of vessels. *Extra-alveolar vessels* are surrounded by lung parenchyma, which acts as a tether or support structure to hold the vessels open. Therefore, lung volume is more important than alveolar pressure for determining the dimensions of extra-alveolar vessels. At high lung volumes, the extra-alveolar vessels are pulled open by tissues outside the vessels. At low lung volumes, this tethering effect is reduced and the extra-alveolar vessels narrow. Also, extra-alveolar vessels have smooth muscle and elastic tissue that tend to collapse the vessels at low lung volumes. The effects of lung volume on

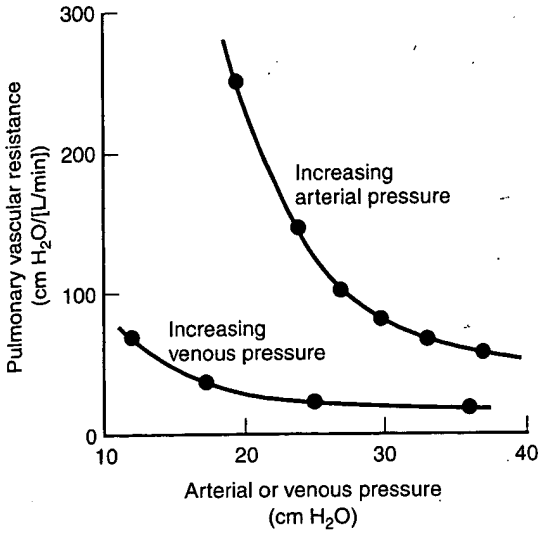

FIGURE 12 Pulmonary vascular resistance decreases with increasing pulmonary arterial or pulmonary venous pressure, while the other pressure is held constant. This is because increasing either pressure increases capillary pressure and causes recruitment and distention of pulmonary capillaries. (After West, Chap. 58 in Fenn and Rahn, eds., *Handbook of physiology, Section 3, Respiration.* Bethesda, MD: American Physiological Society, 1965.)

alveolar vessels are generally opposite those on extra-alveolar vessels. At high lung volumes, the alveolar wall is stretched and becomes thinner, reducing the size of pulmonary capillaries and alveolar vessels. At low lung volumes, the alveolar wall is not stretched and the capillaries relax open to a wider dimension.

Distribution of Blood Flow

The distribution of pulmonary blood flow throughout the pulmonary vascular tree and to different parts of the lung is not uniform. This was first shown in humans with a technique measuring pulmonary blood flow at different heights in the erect human lung using an insoluble radioactive gas. A saline solution containing radioactive xenon was infused in a vein, so the gas would enter the lung in proportion to blood flow (similar to CO_2 elimination from the blood). Radioactive counters were placed at different heights outside the chest to determine relative blood flow rates at different heights in the lung. Relative blood flow increased progressively from top to bottom of the lung.

The effect of gravity on pulmonary vascular pressures is a major factor determining the regional differences in blood flow in the upright human lung. The pulmonary vasculature can be considered a continuous hydrostatic column that is about 30 cm tall in the upright human lung. This means there is a hydrostatic pressure difference of 30 cm H_2O (or 23 mm Hg) between vessels at the top and bottom of the lung. This pressure difference is nearly as large as the pulmonary artery pressure, so it has profound effects on regional distribution of blood flow. Evidence for a gravitational mechanism includes a reduction in the gradient of blood flow in erect persons during exercise when pulmonary arterial pressure increases, and a reduction in the gradient of blood flow in the supine posture. A dorsal-ventral gradient can be measured in people lying supine and the vertical gradient is reversed in persons suspended upside down.

Figure 13 illustrates these effects using the zone model for pulmonary blood flow. This model conceptually divides the lung into three zones to explain how gravity affects blood flow through alveolar vessels at different heights up the lung. *Zone 1* would occur at the top of the lung, where the pulmonary arterial pressure may not be sufficient to pump blood to the top of the lung. In this case, pulmonary arterial pressure is less than the hydrostatic pressure column between the heart and the top of the lung. Alveolar pressure, even if 0, is greater than arterial pressure so the capillaries collapse. Normally, zone 1 does *not* occur because the normal pulmonary arterial pressure (30 cm H_2O) is greater than the height of a water column between the heart and top of the lung (about 15 cm).

Zone 2 occurs near the middle of the lung, where pulmonary arterial pressure is increased by the hydrostatic column, and blood flow occurs. However, venous pressure is less than alveolar pressure because these veins may be below the level of the heart. Intravascular pressure decreases from the arterial to venous level along the capillary, and at some point the alveolar

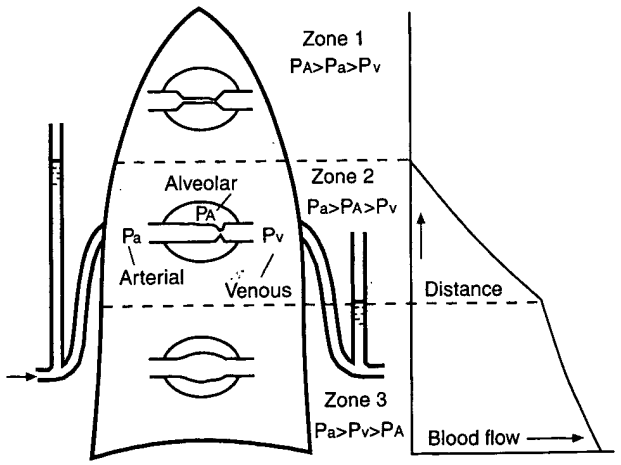

FIGURE 13 West's zone model of pulmonary blood flow predicts increasing blood flow down the lung because of the effects of gravity on pressures, as explained in the text. Pa, arterial pressure; PA, alveolar pressure; Pv, venous pressure. (After West, Chap. 58 in Fenn and Rahn, eds., *Handbook of physiology, Section 3, Respiration.* Bethesda, MD: American Physiological Society, 1965.)

pressure exceeds capillary pressure. This tends to collapse the capillary and reduce flow. If flow actually stops, then pressure in the capillary rises toward the arterial level until the capillary is reopened and flow resumes. In zone 2, the relevant pressure gradient driving blood flow is the arterial-alveolar difference and venous pressure is not important in determining zone 2 flow. Systems with flow determined by upstream and outside (instead of downstream) pressures are called *Starling resistors*. Figure 13 shows flow progressively increasing down zone 2 because the hydrostatic column increases arterial pressure while alveolar pressure is constant. Both capillary recruitment and distention can contribute to increased flow in zone 2.

Zone 3 occurs near the bottom of the lung, where venous pressure is increased sufficiently by the hydrostatic column to exceed alveolar pressure. Therefore, the arterial-venous pressure difference determines blood flow in zone 3. Figure 13 shows flow increasing down zone 3 because the hydrostatic column distends the capillaries. Some data suggest a *zone 4*, with decreased flows at the very bottom of the lung. It was hypothesized that high intravascular pressure leads to edema and vascular compression by the interstitium. However, zone 4 can be measured even after animals are inverted, suggesting that factors other than gravity may be involved.

Other methods of measuring the distribution of pulmonary blood flow suggest that factors other than gravity are important also. Radioactive microaggregates of albumin or plastic microspheres can be injected to the pulmonary circulation and they will lodge in capillaries in proportion to local blood flow. Gradients in blood flow have been measured between the center and the periphery of the lung at a given height up the lung. Local stresses and the anatomic details of vascular branching may contribute to such *intraregional heterogeneity* of blood flow. Intraregional heterogeneity may explain up to half the total heterogeneity of blood flow in the lungs.

Control of Pulmonary Blood Flow

The most important physiologic mechanism that *actively* controls blood flow in the lungs is *hypoxic pulmonary vasoconstriction*. Hypoxic pulmonary vasoconstriction is a direct response of vascular smooth muscle in pulmonary arterioles to decreased alveolar P_{O_2}. The cellular mechanism involves potassium channels in the pulmonary artery endothelium that are sensitive to O_2 level. Hypoxic pulmonary vasoconstriction can be reduced by low concentrations of inhaled nitric oxide (20 ppm NO) in humans. NO also relaxes systemic vessels through a cyclic guanosine monophosphate (cGMP) pathway. Hypoxic pulmonary vasoconstriction is not a reflex response, and it can even be induced in rings of pulmonary arterioles *in vitro*. This is opposite the vasodilatory effect of hypoxia in systemic arterioles.

A direct vasoconstrictor response to local alveolar P_{O_2} allows blood flow to be selectively diverted away from poorly ventilated regions of the lung. Hence, hypoxic pulmonary vasoconstriction is important for matching unequal distributions of ventilation and blood flow throughout the lungs. However, this response might be more important during the transition in the circulatory pattern at birth. Pulmonary blood flow is only 15% of the cardiac output in the fetus. P_{O_2} is relatively low in amniotic fluid, so hypoxic pulmonary vasoconstriction helps keep the pulmonary vascular resistance high in the fetus. At birth, the alveolar P_{O_2} increases with the onset of air breathing, and pulmonary vascular resistance decreases dramatically so the lungs can handle 100% of the cardiac output. Figure 14 shows the effect of P_{O_2} on pulmonary vascular resistance in a newborn animal; note that the main effect of P_{O_2} occurs at very low levels. However, blood pH has an effect even at high P_{O_2}, so the increase in pH with the onset of air breathing will also reduce pulmonary vascular resistance in the newborn.

Other physiologic factors capable of influencing the pulmonary circulation include a weak vasoconstrictor effect from the sympathetic nervous system and potent vasoconstriction by endothelins, which are peptides released by pulmonary epithelial and endothelial cells (e.g., ET-1).

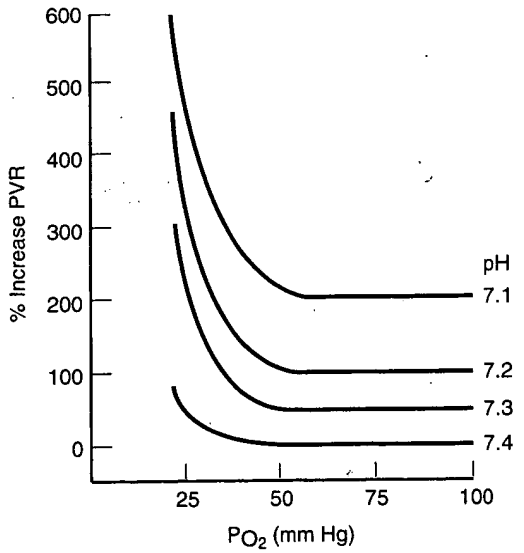

FIGURE 14 Deceasing O_2 in inspired gas (P_{O_2}) causes hypoxic vasoconstriction and increases pulmonary vascular resistance (PVR). Arterial acidosis exaggerates this effect in newborns and may be important in helping toe establish the adult pattern of circulation. (After Rudolph and Yuan, *J Clin Invest* 1966;45:399.)

Lung Fluid Balance

The pulmonary capillaries are extremely thin and contain pores that allow fluid to move across their walls. *Starling's law* describes the forces that govern fluid flux across capillary walls (see Chapter 16), and an understanding of these forces is necessary to understand both normal and pathologic lung fluid balance. Starling's law states that the net fluid flux across the capillary depends on a balance of *hydrostatic forces* (P) and *colloid osmotic* (or *oncotic*) *forces* (π):

$$\text{Net fluid flux} = K_{fc}[(P_c - P_i) - \sigma(\pi_c - \pi_i)],$$

where K_{fc} is *a filtration coefficient* that depends on the total surface area of the capillary and on the number and size of pores in the capillary. Hydrostatic pressure in the capillary (P_c) tends to move fluid out, and interstitial pressure (P_i) tends to move fluid into the capillary. Conversely, capillary osmotic pressure (π_c) tends to hold fluid in the capillary, and interstitial osmotic pressure (π_i) tends to draw fluid out of the capillary. The osmotic reflection coefficient (σ) describes the effectiveness of osmotic pressure at moving fluids, and it can range from 0 to 1. Conceptually, σ compares the size of the pore to the osmotically active solute: $\sigma = 0$ if the solute can move freely through the pore, and $\sigma = 1$ if the solute cannot move through the pore.

Normally, the balance of forces results in net *filtration*, or the movement of a few milliliters per hour of fluid *out* of the capillaries. Normal $P_c \approx 10$ mm Hg and normal P_i in the lungs is subatmospheric so there is a positive hydrostatic force moving fluid out of the capillaries. The *interstitial space* around alveolar capillaries is not compliant, so filtration in this region tends to increase local interstitial pressure. This local pressure increase is thought to provide a gradient moving filtrate toward the interstitium around the extra-alveolar vessels. Filtrate in this extra-alveolar region can be reabsorbed by the bronchial circulation or collected by lymphatics, which also return the fluid to the vascular system.

Normal *plasma protein* concentration is about 7.5 g/dL (mainly albumin); this exerts an osmotic pressure of about 28 mm Hg. The interstitium contains only about 5 g/dL of protein with an osmotic pressure of 15–20 mm Hg. Therefore, the osmotic forces promote absorption. Also, osmotic forces provide a natural feedback system, in which increased filtration dilutes the interstitial space. This reduces the osmotic gradient pulling fluid out of the capillaries. Recall that the osmotic pressure depends on the number of molecules in solution.

When this normal balance of forces is disturbed, filtration can exceed the capacity of reabsorption, and lymphatic drainage and fluid accumulates in the interstitium. *Edema* is the accumulation of excess filtrate outside the capillaries. Pulmonary edema fluid accumulates first in the peribronchiolar and perivascular spaces; this is called *interstitial edema*. Interstitial edema can alter local ventilation and perfusion and make gas exchange inefficient (Chapter 21). *Alveolar edema*, or flooding of excess filtrate into the alveolar spaces, is more serious because it can totally block ventilation and cause blood flow shunts in affected lung regions (Chapter 21). The exact mechanisms resulting in alveolar edema are not known, but they involve exceeding the lung's capacity for lymphatic drainage and changes in solute and fluid transport across airway epithelial cells. Alveolar type II epithelial cells normally transport NaCl to the basolateral surface, and water follows, keeping the alveoli dry.

Edema fluid can have a low or high protein concentration. Hydrostatic edema, which may occur with elevated pulmonary capillary pressures in congestive heart failure, results in filtrate with low protein concentrations. Other lung injuries, such as adult respiratory distress syndrome, may alter the permeability of the capillary endothelium (i.e., changes) and produce a protein-rich edema fluid.

NONRESPIRATORY FUNCTIONS OF THE LUNG

Airway Defense Mechanisms

The exchange surface area of the lung is the largest interface between the body and the environment. Therefore, the lungs have an important set of mechanisms to defend the body from foreign matter. The first line of defense is the *upper airways*, including the mouth and nose. A major function of the upper airways is to warm and humidify air entering the respiratory system, which prevents drying and cooling of the delicate epithelial barrier in the lungs. Complex air passages in the nose, called *turbinates*, also help trap large inhaled particles. Inhaled air enters the *pharynx* from the oronasal cavities, then passes to the *larynx* and through the *vocal cords*, and finally enters the trachea. Food and drink are kept out of the lungs by the *epiglottis*, which moves over the entrance to the larynx during swallowing. The lung is protected from very small particles suspended in the air, called *aerosols*, by three mechanisms. Large aerosols, with diameters of 1 μm or more, are removed from inhaled gas by *impaction* in the nose and pharynx as just described . Impaction traps aerosols when they fail to turn a corner with gas flow, and inertia carries the particle onto a wet mucosal surface. Medium-sized aerosols are trapped in the airways by

sedimentation, as the particles fall out of the airflow under their own weight. Sedimentation occurs in the terminal and respiratory bronchioles because the total cross-sectional area of the airways greatly increases, and the forward velocity of inhaled air decreases (see Fig. 4). This is the area at which most soot and coal dust is deposited. The smallest aerosols, with diameters of 0.1 μm or less, can actually reach the alveoli by *diffusion.*

Particles that deposit in the lungs and airways are removed by two mechanisms. First, *mucociliary transport* removes foreign particles from the conducting airways (Fig. 15). Particles deposited in mucus are moved toward the mouth by the continuous beating of *cilia* on the airway epithelial cells. The cilia beat about 20 times/sec in a coordinated manner to move mucus upward out of the large airways at a speed of about 1–3 cm/min. When mucus reaches the pharynx, it can be swallowed, so deposited particles are removed from the respiratory system. Ciliary function can be impaired by smoking and pollutants such as sulfur and nitrogen oxides. Mucus is actually a complex secretion from the airway epithelium consisting of a gel layer and a sol layer. The top layer, or gel layer, is viscous and sticky to trap particles deposited on the airways. It contains macromolecules, such as *mucin.* The bottom layer is a less viscous secretion that bathes the 5- to 7-μm-long *cilia* on the airway epithelium. Therefore, the cilia can move easily in the sol layer, and the gel layer floating on top is moved up and out of the airways. Diseases such as cystic fibrosis and chronic bronchitis can affect mucous secretion. Second, alveolar *macrophages* provide an additional mechanism for removing particles deposited deeper in the lungs, where the blood–gas barrier must be very thin for gas exchange. Macrophages originate in the bone marrow and circulate in the blood as monocytes before settling in the respiratory zone of the lungs, where the epithelium is not ciliated. They roam the airway surfaces by ameboid action and engulf foreign particles by *phagocytosis.* Most foreign substances are destroyed by *lysozymes* inside the macrophage. However, carbon and mineral particles may be stored in residual bodies in the macrophage, which then settles in the interstitium. The effects of mineral dusts are especially insidious, leading to a progressive destruction of lung tissue, and even lung cancer in the case of asbestosis. Normal macrophages that do not settle in the interstitium leave the lung by the mucociliary transport or the lymphatics.

Neutrophils can leave the pulmonary circulation and provide a secondary line of phagocytic defense in the alveoli. Phagocytes, as well as immune cells (see later discussion), may release reactive oxygen species that can cause tissue damage. However, such damage is limited by the antioxidant glutathione, which occurs in surfactant at levels 100 times higher than in other tissues. Pulmonary cells have evolved efficient mechanisms to

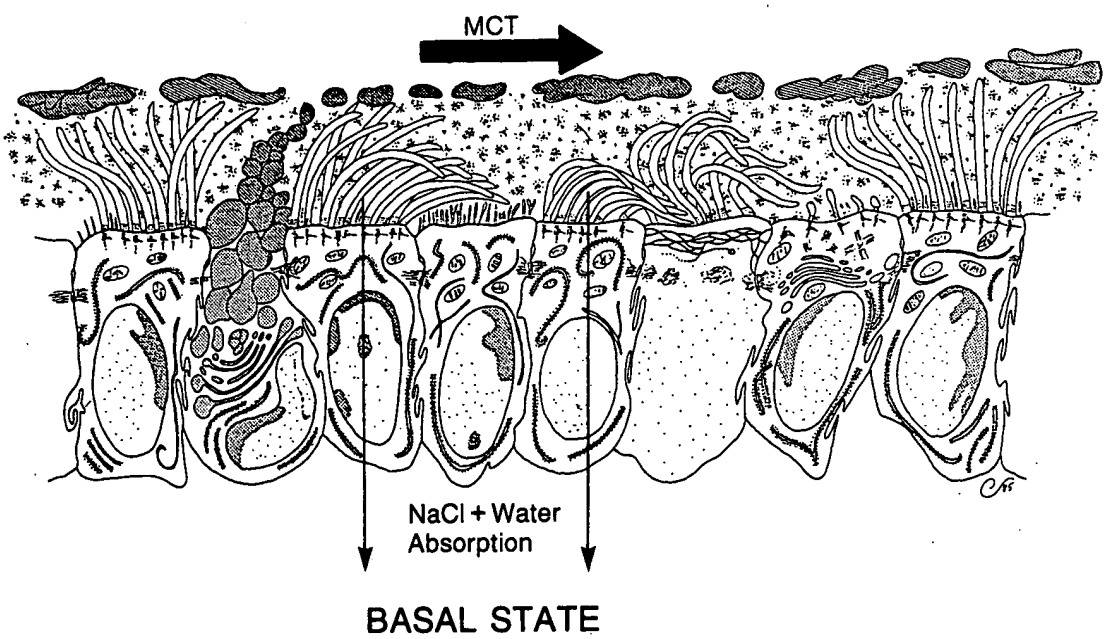

FIGURE 15 Cross-sectional schematic of conducting airway showing ciliated epithelial cells interspersed with mucous secretory cells. Mucociliary transport (MCT) moves the sticky surface layer of mucus (gel layer = shaded globules) up the airways by the beating motion of cilia in the less viscous, lower layer of mucus (sol layer = stars). (From Gabriel and Boucher, Chap. 20 in Crystal *et al.*, eds., *The lung: Scientific foundations.* Philadelphia: Lippincott-Raven, 1997.)

Clinical Note

Cystic fibrosis (CF) is the most common lethal genetic disease in Caucasians (1 in 2500 live births). It involves the lungs, sweat glands, pancreas, intestine, liver, and reproductive system, but pulmonary disease causes 90% of the deaths in CF patients. CF is characterized by abnormally thick mucous secretion, which impairs mucociliary transport in the airways and leaves the lungs vulnerable to bacterial infections. Chronic airway infection leads to abnormalities in gas exchange and the pulmonary circulation and ultimately to death by respiratory failure. Treating gastrointestinal complications and enhancing nutrition is important for preserving pulmonary function in CF. Improved treatment of infections has increased the life expectancy for CF patients from infancy to young adulthood, but recent results offer the promise for curing CF with gene therapy.

Abnormal chloride transport occurs in all tissues affected by CF, and this is explained by mutations in the CF *transmembrane conductance regulator* (CFTR). CFTR is involved in several aspects of mucous secretion in the airways: (1) Normal CFTR acts as a channel for chloride secretion at the apical surface of airway epithelial cells and (2) normal CFTR regulates sodium conductance through different channels by an unknown cell-signaling mechanism. Figure 15 shows that NaCl and water are *normally* absorbed out of the airways, but secretagogues can stimulate NaCl and mucous secretion into the airways. Normally the NaCl pulls water into the sol layer of the mucus so it is not too sticky and ciliary motion is efficient; this process is impaired in CF.

An autosomal recessive mutation results in deletion of a single amino acid from CFTR in 70% of CF patients. This mutant CFTR does not fold properly in the endoplasmic reticulum and it is catabolized before it can be inserted in the cell membrane. New therapeutic trials have tried (1) correcting ion transport by blocking sodium absorption or stimulating sodium secretion with non-CFTR mechanisms, (2) reducing the stickiness of mucus with enzymes, and (3) rescuing mutant CFTR from defective cell trafficking and stimulating normal membrane insertion. However, the most exciting possibility is that of introducing a normal copy of the CFTR gene into the airway in early life. Lung epithelial cells are easily accessible to gene transfer agents and adenoviruses have been used to deliver normal CFTR and restore chloride secretion in the nasal mucosa of patients for up to 3 weeks. Airway submucosal glands, which are normally rich in CFTR, are not as accessible to such gene transfer. Hence, the future of this therapy depends on delivering the gene to enough cells in the respiratory tract to normalize function throughout the airways and on lengthening the duration of expression of the normal gene product.

defend against oxidant injury, presumably because P_{O_2} is so high in the airways compared to other body compartments.

Immune System Defense Mechanisms

The lung is similar to all other organs by containing *lymphocytes* (T and B cells) in the interstitium. These defense cells originate from the bone marrow and lymph nodes and respond to foreign invaders with cellular (acquired antibody) mechanisms. Dendritic cells present antigens to the lymphocytes. Considering that up to 10^{10} antigenic particles may reach the alveoli every day, the challenge for the pulmonary immune system is to process this foreign material and not overamplify an inflammatory response. Basic immune mechanisms in the lungs are similar to the rest of the body and are not covered here.

Lymphatics are the main pathway for removal of immune cells that have already responded to foreign substances or cells in the lungs. The lymphatic drainage also removes excess fluid filtration from the pulmonary capillaries as described earlier. Pulmonary lymphatics start as blind end vessels in the acini, where they collect fluid and lymphocytes through a leaky endothelium. Lymphatics do not occur at the level of the alveoli. Lymph flow is always directed out of the lungs by numerous valves in a network of vessels that generally follows the large airways and blood vessels. *Lymph nodes* occur along this network and function as biological filters. Macrophages and immune defense cells collect in lymph nodes and present antigens to immunocompetent cells in the nodes. This programs new immune system defenses for future invasions. Ultimately, pulmonary lymph returns to the venous system near the junction of the subclavian and jugular veins.

Biosynthetic Functions

The lung is ideally situated to carry out many biosynthetic functions on substances in the blood because it receives the entire cardiac output. Three major mechanisms are used by the lung to process substances in blood: (1) synthesis or addition, (2) degradation or removal, and (3) activation or conversion, i.e., biotransformation. Table III summarizes the effect of the lungs on substances in blood that pass through the pulmonary circulation.

Biogenic amines are removed from the pulmonary circulation in varying degrees. *Serotonin* (or 5-hydroxytryptamine) occurs in the lungs as a product of alveolar macrophages and pulmonary mast cells, in addition to arriving by the circulation. A carrier-mediated uptake process in the pulmonary endothelium almost completely removes serotonin from the blood. *Norepinephrine* occurs in the lungs from local activation of sympathetic nerve endings. Norepinephrine is removed from the blood by a carrier-mediated process into pulmonary endothelial cells, which contain enzymes to degrade the neurotransmitter. However, this pulmonary uptake mechanism is not effective at controlling systemic norepinephrine levels. *Histamine* is stored in large amounts in pulmonary mast cells in the airway walls and epithelium. Histamine can be released from these cells by allergic reactions and causes bronchial smooth muscle contraction and pulmonary vasoconstriction. Enzymes for degrading histamine occur in the lung, but the pulmonary circulation is not effective at removing histamine, perhaps because a cellular uptake mechanism does not occur.

Peptides are degraded or activated by the pulmonary circulation. *Angiotensin II* is a vasoconstrictor produced in the lungs by *angiotensin-converting enzyme* (ACE). ACE occurs in pulmonary capillary endothelial cells and creates angiotensin II by cleaving two amino acids from a precursor decapeptide called angiotensin I. Angiotensin I is not a strong vasoconstrictor and it is not changed by the pulmonary circulation. ACE is the main example of activation by the pulmonary circulation and it is extremely effective, with almost 100% conversion in a single pass of the blood through the lungs. *Bradykinin* is a potent vasodilator that is not synthesized in the lung, but is largely inactivated by the pulmonary circulation. Enzymatic inactivation of bradykinin occurs at the same endothelial site and uses the same enzyme (ACE) used to activate angiotensin I.

Arachidonic acid metabolites, also called *eicosanoids*, are either almost completely removed from blood by the pulmonary circulation or they are not affected. Arachidonic acid is made in the lungs and other tissues by breakdown of phospholipid membranes. *Prostaglandins* (PG) and *thromboxanes* (Tx) are synthesized from arachidonic acid by cyclo-oxygenase and peroxidase, and can be released in pathologic states such as embolism and anaphylaxis. $PGF_{2\alpha}$ is a bronchoconstrictor and vasoconstrictor, PGE_2 is a vasoconstrictor, and PGE_1 is a vasodilator, but they affect only the local airways and vessels where they are produced because they are metabolized by the pulmonary circulation. TxA_2, a bronchoconstrictor, vasodilator, and platelet-aggregating substance, is also metabolized by the pulmonary circulation. On the other hand, PGI_2 (or prostacyclin), which is a vasodilator and inhibitor of platelet aggregation, is not affected by the pulmonary circulation so it can exert systemic effects also.

Leukotrienes (LTs) are synthesized from arachidonic acid by a different pathway, and they are part of the airway inflammatory response. LTC_4, LTD_4, and LTE_4 may play a role in asthma. These LTs are 1000 times more potent than histamine as bronchoconstrictors, they stimulate mucous production, and they increase vascular permeability, which can lead to edema. LTB_4 induces leukocyte chemotaxis, increased vascular permeability, and vasodilation. LTs are removed almost completely by the pulmonary circulation, so their effects are local.

TABLE III Effect of the Pulmonary Circulation on Substances in Blood

Biogenic Amines
• Serotonin: 95% removed
• Norepinephrine: Up to 40% removed
• Histamine: No change
Peptides:
• Angiotensin I: Converted to angiotensin II by ACE
• Angiotensin II: No change
• Bradykinin: Up to 80% inactivated
Arachidonic Acid Metabolites:
• Prostaglandin E_1, E_2, F_{2a}: 90% removed
• Prostaglandin A_1, A_2: No change
• Prostacyclin (PGI): No change
• Leukotrienes: 90% or more removed
• Thromboxane: Removed

Suggested Readings

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APPENDIX TRANSLATION OF REFERENCE 3

Bulletin of the Medical School of Shantou University, 1994(2):77-78

THE CLINICAL USE AND DOSAGE FORM OF IODOPHORS

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Iodophor (also known as povidone iodine) is an antiseptic comprising a surfactant as carrier complexing with the element iodine. When contacting with the iodophor, the cytoplast and the molecules of the biologic active substances in the cytoplast such as mercapto-containing compounds, peptides, proteins, enzymes, lipids, and cytosine, etc., will be oxidized or iodinated, and then will lose activity. In this way, the object of sterilization is achieved. Iodophor is a claret flavourless clear solution, soluble in water and alcohol. Its aqueous solution is stable with pH of 3-4, and is used as a new antiseptics with wide antibacterial spectrum. Since 1980s', iodophor (povidone iodine) has been widely used in the sterilization and treatment of surgery, O&G, stomatology, dermatology, otorhinolaryngology and the like in developed regions such as Europe, U.S., and Japan. Furthermore, it has been widely used in all field and people's daily life. In the Western countries, it is often used in preventing and treating various venereal diseases and HIV; it is also used by NASA for sterilizing the body of astronaut, clothes, and spacecraft when the spacecraft and space shuttle return to earth, so as to kill any possible microorganism from outer space. It is a new agent and antiseptics in China. Its features, clinic use, dosages forms and present application in China are described hereafter.

I. FEATURES

1.1 Iodophor is a powerful and wide spectrum antiseptics

Providone iodine is outstandingly active on killing various bacteria, virus, and fungus such as HB virus, HA virus, Bacillus subtilis black variant spore, Staphylococcus aureus, Bacillus coli, Aeruginosus Bacillus, Influenza virus, Diploccoccus of Neisser, Syphilis Spirochete, and HIV, etc., without any drug tolerance. HIV is destroyed in 2 min with 35 PPM; HB surface antigen is entirely destroyed with 250 PPM for 5 min, or with 500 PPM for 2 min; Bacillus subtilis black variant spore is destroyed when the effective iodine concentration is over 200 PPM; propagula taphylococcus aureus and Bacillus coli are entirely destroyed in 2 min with 20 PPM; Aeruginosus Bacillus is entirely destroyed in with 250 PPM fro 1 min; various dishware will be sterilized according to the relative requirements with15 PPM for 5 min.

1.2 Iodophor can be widely used in various fields

Being effective for a long period, it can be administered directly on wound surface and mucous membrane without irritation and burning sensation. It can be used for sterilization of the skin before surgery, washing vomica, treating burned surface, and sterilization of the mucous membrane of oral cavity, eye, urinary system and genital system. In addition, it can be used for sterilization of the stuff in hospital such as surgery equipment, endoscope and the like, fruits, dishware, and public environment, and for prevention of epidemics.

1.3 Iodophor is soluble in water

When applied to skin or cloth, it can be easily removed by water instead of alcohol.

1.4 The effect of Iodophor will not be influenced by blood plasma, blood, soap, liquor puris etc.

1.5 Iodophor is safe for human without obvious adverse and toxic effects

After experiments, the Environment Monitor Institute of Chinese Academy of Preventive Medicine provides the following results: LD50>5000mg/Kg body weight; so Iodophor has no toxicity; no mutagenicity; no pollution; and will not be absorbed by human body to induce iodine poisoning; safe and convenient for use.

1.6 Iodophor has sanitary function at the same time of sterilization

2. *CLINICAL USE*

2.1 wide use in sterilizing skin and mucosa in surgeries and sterilization of injection site replacing iodine tincture. For examples, a solution of 1000 PPM is applied on the skin.

2.2 use in sterilizing medical instrument. For example, the instrument is soaked in a solution of 200PPM-250PPM for 30 min (the instrument made of copper, lead, and silver should not be soaked for long time). After sterilization, the instruments are washed by water or dried to reduce erosion.

2.3 use in sterilizing hands of physicians. For example, wash with 50-100 PPM.

2.4 application on suppurated skin, wounded skin, mucosa, burned skin, changing dressing, etc. with a solution of 3000 PPM for sterilization.

2.5 use in lavage and treatment of abortion, coleitis, etc., with a solution of 250 PPM.

3. *DOSAGE FORMS*

3.1 The aqua thereof can be diluted to various concentrations depending on sections to be sterilized.

3.2 The tincture form will dry quickly, and thus is suitable for sterilizing surgery region of urgent operation. It is not suitable for mucosa and wound because of comprising alcohol.

3.3 The collutory thereof is used for mouthwash to treat inflammation of oral cavity, throat and gum.

3.4 The ointment form is suitable for burned skin, chronic ulcer of skin, bed sore, trauma infection and the like. According to the report of Empyrosis Department of the First Hospital Affiliated with Zhongshan Medical University and the clinic investigation of Empyrosis Laboratory of 159 Hospital of the PLA, said form will hardly induce drug-resistance; the wounded surface dried quickly; the crust is intact; and said form has no irritation to the wounded surface. Said form is suitable for the patients who are allergic to sulfanilamide.

3.5 The aerosol form can be sprayed evenly on the wounded surface by a nebulizer. It is suitable for the wounded surface with large area, and stitched surgery wound which is covered with dressing after being sprayed. In particular, it is suitable for the wounds which can not be directly touched.

3.6 The vaginal suppository is suitable for the gynecologic diseases such as infusorian, monilia, bacteria coleitis, non-specific cervical erosion and the like. Each dose is administered in morning and night respectively.

3.7 The aqua containing soft soap is used for washing hands of physicians, preparing the surgery region for operation, washing hair, antepartum examination and washing perineum after parturition. The patients suffered from tinea capitis can wash hair with said form for treatment.

3.8 The solid iodophors form is invented by Chemical Department of Nanjing University. It is packed in form of solid powder, and can be formulated into solutions with various concentrations to meet practical requirements.

4. *PRESENT APPLICATION IN OUR COUNTRY*

Although iodophors has excellent properties and wide antibacterial spectrum, it is not widely used in China presently. Many physicians are not certain about its sanitary effect because it has not a smell like lysol solution. It is not advisable to judge the

sanitary effect of iodophors which is flavourless by "sanitary smell". Any way, this new antiseptic has not been widely used in China (although it has been permitted to be used by Health Ministry and be collected into the China Pharmacopeia, 90 Edition).

碘伏的临床应用及剂型

蔡小燕

碘伏（Iodophors）也称聚维酮碘、皮维碘。是一种以表面活性剂为载体与元素碘络合而成的消毒剂，当细菌胞质和胞质中的巯基化合物、肽类、蛋白质、酶、脂质和胞嘧啶等生物活性物质的分子与之接触后，立即被碘氧化或碘化，使之丧失活性，从而达到杀灭细菌的作用。碘伏为深棕红色水溶液，无味、无混浊，可与水混溶，溶于乙醇，其水溶液性质稳定，pH3～4，是一种新型广谱杀菌消毒剂。自八十年代起，碘伏已在欧、美、日本等发达地区广泛应用于外科、妇产科、口腔科、皮肤科和耳鼻咽喉科等的消毒与治疗，并已推广到各行各业及人们的日常生活中，西方各国已广泛用于防治各类性病及爱滋病。美国太空总署亦专门选定碘伏作为宇宙飞船、航天飞机返回地面后宇航员的身体、衣物及航天器的消毒，以杀灭太空中可能带来的一切微生物。我国近几年才开始研制及生产，是国内较新的治疗、消毒药。本文就其特性、临床应用、剂型演化及在我国的应用现状作一报告。

1 特性

1.1 高效、广谱。对乙型肝炎病毒、甲型肝炎病毒、枯草杆菌黑色变种芽胞、金黄色葡萄球菌、大肠杆菌、绿脓杆菌、流感病毒、淋病双球菌、梅毒螺旋体、爱滋病毒等各类细菌病毒、真菌有强大的杀灭力，并不产生耐药性。对爱滋病毒，35PPM 2min 灭活，对乙肝表面抗原 250PPM 时 5min，500PPM 时 2imn 可完全灭活。当有效碘浓度超过 200PPM 时可即杀死枯草杆菌芽胞，对繁殖体金黄色葡萄球菌、大肠杆菌浓度在 20PPM 时可在 2min 内完全灭活。浓度在 250PPM 时 1min 能杀灭绿脓杆菌。15PPM5min 各种餐具消毒达标[1]。

1.2 应用范围广。能直接接触创面及粘膜，而无刺激性及烧灼感，作用持久。除可作医院医生、护士术前皮肤及手术野消毒外，还可用于脓腔冲洗，烧伤创面的治疗，口腔、眼、泌尿生殖粘膜的消毒。此外，亦可用于手术医疗器械、内窥镜、医院其它物品的消毒，对水果、餐具、公共卫生环境的消毒及传染病预防等。[2]

1.3 具水溶性，涂布于人体皮肤或污染衣物后，不须酒精去碘，用自来水清洗即可除去。

1.4 不受血浆、血液、脓液、肥皂等影响而减轻其疗效。

1.5 对人体安全，无明显毒副作用，经中国预防医学科学院环境监测研究所实验证明，LD50＞5000mg/Kg 体重，实属无毒物质，无致突变性，无污染，不会被人体吸收而致碘中毒，使用安全方便。

1.6 具有一定的清洁功效，消毒去污一次完成。

2 临床应用

2.1 取代碘酊，广泛应用于各种大、小手术进行术野皮肤，粘膜消毒，注射部位消

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毒。可用1000PPM溶液擦试。

2.2 医疗器械消毒，可用200～250PPM溶液浸泡30min（铜、铅、银质器具不宜长期浸泡）。消毒后用水冲洗或擦干，可减轻腐蚀度。

2.3 医务人员的手消毒，可用50～100PPM溶液洗刷。

2.4 化脓性皮肤病，感染的伤口、皮肤粘膜、烧伤创面的消毒，换药等可用3000PPM溶液涂擦。

2.5 人流和慢性阴道炎及其它腔道的冲洗和治疗可用250PPM溶液。

3 剂型演化

3.1 水剂可按不同的消毒部位稀释成各种浓度的溶液应用。

3.2 酊剂 涂布于皮肤后快干，故适用于紧急手术时手术野之消毒用。因含有酒精，故不宜用于粘膜及伤口。

3.3 漱口液 用于治疗口腔炎 咽喉炎、牙龈炎时作含漱用。

3.4 软膏剂 适用于烧伤、皮肤慢性溃疡、褥疮及外伤感染等。据中山医科大学附属第一医院烧伤科报道及解放军159医院烧伤科实验室的临床观察，使用后细菌对其不易产生抗药性，创面干燥快，痂皮完整，对创面无刺激性。对碘胺药过敏的病人可使用此药治疗。

3.5 气雾剂 按喷洒装量后可均匀喷洒于病灶上，适用于大面积烧伤创面喷洒，手术伤口缝合后喷洒再加盖敷料，特别适用于不能直接碰触之伤口。

3.6 阴道栓剂 适用于滴虫、念珠菌、病毒、细菌性阴道炎，非特异性子宫颈糜烂等妇科疾患作栓塞用，早晚可用一粒。

3.7 含软皂水剂 医护人员洗手，术前术野的准备，毛发洗涤，产妇产前检查及产后清洗会阴用。头癣患者可用于洗头作治疗之用。

3.8 固体碘伏 由南京大学化学系在国内首先研制成功。为固体粉末包装，可根据需要自由调配成不同浓度的溶液[3]。

4 碘伏在我国应用现状

尽管碘伏有其优良的特性及高效广泛的消毒杀菌效果，但在我国的应用目前仍不是很普遍。因其没有像来苏尔、臭药水那样的"消毒气味"，至今仍有不少医护人员怀疑碘伏的消毒作用，担心消毒不彻底。以"消毒气味"来判断碘伏这种无臭无味的消毒剂的消毒程度是不恰当的。加上使用习惯等因素，碘伏作为新一代消毒剂目前在我国仍未能得到普遍推广应用（尽管国家卫生部早已批准使用并被90版中国药典收载）。

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张庆英出席全国营养学术会

全国首届营养学术会议于10月5日至15日在大连举行。我院卫生学教研室青年教师张庆英应邀出席会议，并宣读题为《汕头市大学生营养状况调查》的学术论文。

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